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THE MOUNT SINAI JOURNAL OF MEDICINE

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In Memoriam:

Fenton Schaffner, M.D.

December 8, 1920–January 24, 2000

Dr. Fenton Schaffner.

Dr. Fenton Schaffner, an internationally renowned hepatologist who made pioneering discoveries in the field of liver diseases and was a distinguished member of the Mount Sinai community for more than forty years, died at his home in Washington, Connecticut, on January 24, 2000.

Born in Chicago, Dr. Schaffner earned BS and MD degrees at the University of Chicago and an MS degree from Northwestern University. After serving as a physician in the United States Navy, he returned to Chicago, where he joined the faculty of Northwestern University School of Medicine and practiced internal medicine. He also began an extraordinarily productive collaboration with Hans Popper that lasted for four decades and brought hepatology to the forefront of the intellectually active disciplines of medicine. Following his friend and colleague, who had been appointed to the directorship of the Department of Pathology at The Mount Sinai Hospital, Dr. Schaffner accepted a position at Mount Sinai, in 1958, to establish the Division of Liver Diseases and to serve as its first director. Mount Sinai opened its medical school in 1968, and Dr. Schaffner was among its first distinguished faculty members. During his exceptional career at the Mount Sinai School of Medicine, he held full professorships in both medicine and pathology, and was acting chairman of the Department of

Medicine from 1972 to 1974. Dr. Schaffner was named the George Baehr Professor of Medicine in 1973 and held that distinguished chair until his retirement in 1991.

Dr. Schaffner was an astute clinical observer, and his extensive clinical practice was the source of many of his insights, which were amplified by his expertise in light and electron microscopy. Although his clinical knowledge was virtually encyclopedic, he was especially interested in primary biliary cirrhosis, chronic hepatitis, and hepatic injury from drugs, areas to which he made important scholarly contributions. A clinician-scientist, he never lost sight of the primary responsibilities of a physician. His commitment to patient care was evident in his extraordinary devotion to each of his patients. A master clinician who attended to the needs of individual patients from around the world, he was also devoted to advancing the delivery of quality health care and held the position of governor of the New York Downstate Chapter of the American College of Physicians.

As a founding member of the American Association for the Study of Liver Diseases (AASLD) and an early supporter of the International Association for the Study of the Liver, Dr. Schaffner's impact on the field of hepatology has been global and enduring. He served as secretary of AASLD for fifteen years and was elected its president in 1976. He was also a vigorous supporter of the American Liver Foundation (ALF). His early support and leadership came at a critical time in the evolution of ALF, and continued throughout his life. Working to bridge the inter-institutional rivalries that had characterized the New York scene, he was one of the founders of ALF's highly successful Greater New York Chapter. The Chapter honored him in 1997 with the Mary Lea Johnson Richards Research Institute Award.

The author or co-author of more than 400 papers and books, Dr. Schaffner was recognized as an exceptional educator, teacher, and innovator in the study of liver diseases. His devotion to the dissemination of knowledge and specifically to the education of physicians was exemplified by his role in co-editing the classic series *Progress in Liver Diseases* over a 29-year period. He was also appointed one of the first associate editors of *Seminars in Liver Disease* when that journal was founded in 1980, participated regularly in its annual editorial board meetings for two decades, and remained active in this capacity virtually until his death. Dr. Schaffner's legacy, however, is not measured solely by the extraordinary volume of his scholarly contributions. It survives in the many fellows whom he trained, and who now represent a community of senior hepatologists both at Mount Sinai and around the world.

Dr. Schaffner is survived by his wife, Rosanne Kerby Schaffner, and four children, Roberta Schaffner of Dallas, Texas, Dr. John Schaffner of Rochester, Minnesota, Dr. Andrea Schaffner of Madison, Connecticut, and Marjorie Schaffner of Chicago, Illinois. He is also survived by five grandchildren, and a brother, Gerald Schaffner of San Diego, California.

Paul D. Berk, MD
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Clinical Trials in Developing Countries:

A Review of the Moral Issues

DOUGLAS P. LACKEY, PH.D.

Abstract

Several ethicists have raised criticisms of various placebo-controlled clinical trials conducted in developing countries between 1995 and 1998. This essay reviews and rejects the arguments that these trials violated basic canons of medical ethics, or constituted exploitation by scientists in advanced countries of subjects in developing countries. A uniform international standard for the evaluation of such trials is proposed, replacing the old standard of voluntary and informed consent with a more focused standard of uncoerced and undeceived consent.

Key Words: Clinical trials, developing countries, moral issues, ethics.

THE SEPTEMBER 18, 1997 ISSUE of *The New England Journal of Medicine* exploded like a bombshell over the medical ethics community. Not since Harry Beecher's assault in 1966 on the ethics of clinical research scientists (1) had such accusations been hurled about on those cream-colored pages. The subject in question was the conduct of fifteen clinical trials in developing countries (2–5), trials that typically included a placebo arm. Critics charged that patients in placebo arms had been denied needed medical treatment, contrary to medical ethics and to international conventions governing such studies. The article presented the spectre of Western scientists looking for quick publication and Western drug companies looking for quick profits, of exploitation of weak governments and impoverished people by the strong and heartless. The most disturbing charges were pressed vis-à-vis trials for new therapies to block transmission of HIV from mother to child. Expectant mothers in active trial arms got azidothymidine (AZT); expectant mothers in placebo arms got nothing. Had the trials been conducted with two active arms, it was charged, hundreds of cases of infant HIV infection could have been prevented. For physicians to permit such events seemed to violate elementary canons of human morality.

The "Sounding Board" case for the prosecution was made by Drs. Lurie and Wolfe from the Public Interest Health Research Group (6); the ethics of the trials was defended (two weeks later) by Drs. Varmus and Satcher from the NIH and the CDC (7). *The New England Journal of Medicine* itself, which might have been expected to maintain some neutrality between the warring camps, assigned an editorial to Associate Editor Marcia Angell, who weighed in heavily on the side of Lurie and Wolfe (8). Angell compared the controversial trials to the Tuskeegee syphilis study (9, 10), suggesting that researchers conducting the trials were engaged in acts of racist condescension (11).

The controversy subsided somewhat in 1998, when most of the AZT studies ended, with hasty proclamation of successful results (12). Through 1999, further controversy

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Adapted from a presentation made at the Oxford-Mount Sinai-King's College Conference on Bioethics at The Mount Sinai School of Medicine, New York, NY on April 14, 1999.

simmered over revisions in international guidelines (Declaration of Helsinki) governing such trials. Supporters of the trials, which were prima facie inconsistent with the Helsinki guidelines (13), wanted the rules weakened (14); opponents of the trials naturally wanted them tightened (15). The felicitous discovery in 1999 of an effective, practical, and inexpensive drug for the prevention of maternal transmission of HIV (16) provided a final vindication or condemnation of the 1997 studies, depending on one's point of view.

Though these studies are completed, the philosophical issues raised during the controversy remain unresolved. They may bedevil future campaigns against medical problems in developing countries. It is my purpose to consider the general form of the objections raised against the AZT trials and to subject them to the philosophical analysis that this cooler moment makes possible.

The Question of Equipoise

Dr. Angell's editorial (8) begins, ". . . an essential ethical condition for a randomized clinical trial comparing two treatments is that there be no good reason for thinking one is better than the other." She goes on to argue that since the efficacy of "long course" treatment with AZT in reducing maternal transmission of HIV was known (17), a short course of AZT could be presumed to be more effective than placebo. Thus, in the AZT studies in question, which typically compared a short course of AZT against placebo, one of the trial treatments was "known to be better" than the other, contrary to Angell's moral requirement.

The moral rule of epistemological indifference or "equipoise" in clinical trials was introduced into medical ethics by the late Prof. Benjamin Freedman in 1987 (18). It has often been invoked, but rarely examined. To begin with, the rule refers only to treatment studies and not to basic science (e.g., physiology) studies, where the rule cannot apply. So if researchers are doing a mixed study which is part treatment and part basic science, it is possible that the rule may not apply there either.

Let us assume that we are looking at a pure treatment study, one that compares established drug A with experimental drug B for condition c. It may be known that, for the average patient, drug A is a more effective treatment than drug B for condition c. However, drug A may have certain side effects that make it dangerous for a certain subgroup. It is important to know, then, how much less effective drug B is than drug A, in order to get a fix on whether drug B is recommendable, all things considered, for members of the subgroup, who on safety grounds should not be randomized into the trial. Here the rule of equipoise is justifiably broken.

Consider the case in which drug A is known to be more effective than drug B, but drug B is considerably cheaper than drug A. In a society with limited resources, we can assume that there is a fixed budget for dealing with condition c. The question for such a society, and this is a moral question as much as an economic one, is whether a fixed number of dollars will save more lives, or more years of life, or more quality years, if put into drug A or put into drug B. We cannot answer this unless we know precisely how much less effective drug B is than drug A. We have here social equipoise between two strategies for dealing with a health problem, but we do not have medical equipoise for the subjects in the study comparing drugs A and B.

Next consider a trial of behavior modification to reduce HIV infection. Suppose that there is a vaginal gel with known antiviral efficacy and there are condoms of known efficacy in preventing transmission, and that a woman stands a better chance of not becoming infected if she imposes condoms on her partner than if she uses the gel alone. Suppose, furthermore, that it is not known what fraction of the men, in the natural setting, can be persuaded to use condoms, and what fraction of the women can be persuaded to use the gel. In order to know which strategy is best for reducing HIV infection, how dollars for supplies and time for educational efforts are to be invested, we must run a test of condoms-versus-gel versus condoms-plus-gel, contrary to the rule of equipoise.

In an ideal world there will always be enough money for the medically superior treatment, always enough time for the educational efforts that will persuade everyone to use it. Even in a less-than-ideal world that is a bit better than this one, wise political leaders will transfer funds allocated to the purchase of tanks and landmines to the prevention of TB, AIDS, and malaria. But this is not an option for clinical researchers, unless they happen to be running a country along with a clinic. Morally, they must make their best guess about available resources, and proceed with that as a given. In underdeveloped countries, where health budgets may average one dollar per year per capita, it is crucial to know, when a treatment is effective but expensive, whether one tenth of the drug will have one tenth the effect, or one hundredth, or one half. One cannot know this without testing sub-optimal regimens.

Finally, note that the rule of equipoise says that a treatment trial is immoral when I give B rather than A, when I know that A is better than B. But whatever ethical principles make it immoral for me to give B rather than A if I know that A is better, would make it somewhat immoral for me to give B rather than A if I sincerely believe that A is better, since our choices are governed by our beliefs. It follows that a clinical trial would be immoral if the researcher sincerely believes that one treatment is more effective than another (on the basis of anecdotal evidence, scientific logic, clinical experience, or whatever). It is my impression that most researchers conduct trials sincerely believing their pet drug will work. A consistent application of the rule of equipoise would eliminate from science all researchers who happen to be optimists.

The Victims on Placebo

Before there was ever a controversy about trials in developing countries, there were controversies about the use of placebos and sub-optimal regimens in clinical studies (19). Beecher, in 1959, noted that the use of placebos was contrary to the Nuremberg Code, strictly construed (20). Most clinical researchers are also physicians, and the presence of persons on placebo in a trial tugs at the duty, or at least the impulse, to treat. Various gimmicks in trial designs containing placebos have been proposed to reconcile therapeutic compassion with scientific objectivity (21, 22), but none has caught on. Researchers/physicians can console themselves with the thought that, in a double-blind placebo-controlled trial, they do not know, in face-to-face situations, whether a given subject is going without treatment. But this form of ignorance is not bliss.

The 1996 version of the Declaration of Helsinki (23) stipulates that in the case of therapeutic research, "every patient, including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method." It follows that only two sorts of trials are morally permissible: (a) if there is a disease for which there is no therapy, then one can run treatment B against placebo; and (b) if there is a disease for which treatment A is standard, then one can run treatments A plus B against treatment A alone. But few diseases have no therapy, and in many trials one cannot give subjects both treatments A and B because of interactions between A and B.

The majority of trials, of scientific necessity, will pit A versus B or B versus placebo. In the case of the AZT trials, the design favored by the researchers was the "short course" of AZT versus placebo (Design S); the design favored by the critics was the "long course"; of AZT versus the "short course" of AZT (Design L). The troubling argument against Design S was that some infected mothers placed in the placebo arm transmitted HIV to their infant children, and that some of these transmissions could have been prevented had these mothers received AZT. But if this is a moral criticism of design S, it is equally a moral criticism of design L. If you have one trial arm with expectant mothers receiving the short course and one trial with expectant mothers receiving the long course of AZT, then you know that there will be some HIV transmissions in the short course arm that would have been prevented if those very subjects had received the long course. The only method in which you have no preventable transmissions of HIV is to give everyone the long course, and if you do that, you have no trial at all.

Design S and Design L both involved procedures such that, if researchers had behaved differently, there would have been fewer infants infected with HIV. But it is also true that if critics of the trials had donated all their personal savings toward the purchase of AZT, which could be distributed in war-torn countries by Médecins sans Frontières, fewer infants in the world would be infected with HIV. Likewise, fewer infants would be suffering in developing countries if I had donated $200 to CARE today rather than spending that sum (as I did) on a complete set of Haydn symphonies on CD. If we criticize the researchers who conducted these trials for not doing everything they could to prevent vertical transmission of HIV, the same criticism can be laid at our own doorsteps. There are some ethicists, Peter Singer most prominently, who have argued that morality demands that some large fraction of the incomes of persons in developed countries be transferred to persons in poorer countries, where each dollar can do more good (24). Few have agreed with Singer that an action is morally acceptable only if it reduces human suffering more than every other alternative act. The world is full of crimes, but buying Haydn symphonies does not seem to be one of them.

The permissibility of placebo arms in studies is related to the permissibility of conducting natural history studies of medical problems (25). Suppose that an enterprising epidemiologist applies for a grant to determine precisely the natural transmission rate of HIV from mother to infant in selected African villages across a wide stretch of territory. Suppose that the study involves only HIV testing and questionnaires, that the epidemiologist is not trained or equipped to treat HIV infection, and that the peripatetic nature of the work precludes treatment of cases in villages left behind. Isn't it morally permissible to fund such a study? Why not?

Consider now a treatment study of maternal HIV transmission with two active arms. Since everyone gets treatment, the critics are silent, or at least happier than they would be if there were a placebo arm. Suppose everyone agrees that there are no moral problems with the study, at least as regards trial design.

The natural history study is morally permissible. The "active only" study is morally permissible. But what is a double-blind, placebo-controlled trial but a natural history study combined with an active treatment study? If it is morally permissible to run the two studies side by side, is it not equally permissible to run the two studies with a common pool of subjects, randomized into one or the other? If it is morally permissible to enter subjects into "study A or study B," how can it be morally wrong to enter subjects into "study arm A or study arm B?"

The "Standard of Care" Principle

Those who defended the AZT trials occasionally appealed to what has become known as the "Standard of Care" principle: that a clinical trial which meets all other moral standards is morally permissible if and only if it does not deprive subjects of any medical care they would have received if there had been no trial (26).

In the case of the AZT studies, subjects in placebo arms did not receive AZT. But if there had been no trial (so the argument goes), these subjects, given social conditions, would not have received AZT anyway. By contrast, subjects in the Tuskegee syphilis study were deprived of penicillin that they would have received (so the argument goes) had there been no trial. In Tuskegee, the "standard of care" requirement was not met.

It is immediately obvious that the Standard of Care principle is entangled in hazy counterfactuals and foggy empirical claims. A subject in the Ivory Coast AZT trial, had there been no study, might have gotten access, in some way or other, to therapeutic AZT. On the other hand, a subject in the Tuskeegee study might never have gotten penicillin even if there had been no study, because of poverty, ignorance, or bad luck. There is a delicate dance here between the concepts "could" and "would" (27). The Ivory Coast subjects could have gotten AZT (the stuff existed) had there been no trial, but what they actually would have gotten had there been no trial is anyone's guess. The Tuskeegee subjects could have gotten penicillin (the stuff existed), but what they would have gotten had there been no study is also anyone's guess. It is difficult to set up the Standard of Care principle so that it slices cleanly between the AZT studies and the Tuskeegee study, our paradigm case of American research evil.

Notice that in our struggles with the dizzying problem of "what would have happened if things had been different," our ability to predict improves as the difference between the actual world and the hypothetical "different" world diminishes. Thus, opponents of the trials argue that if you have a subject in the placebo arm of a trial, you can predict what would happen if she had not been in the placebo arm: she would have been in the active arm and would have gotten AZT. But here one is not comparing a world in which there is a trial with a world in which there is no trial, and that is the proper comparison to make when you pass moral judgment on the trial. It seems that when we have the right comparison, we can make no judgment, and when we can make a judgment, we have the wrong comparison. This is not a good basis for making policy (28).

Instead of the Standard of Care principle, we should consider here the more general moral principle that we should do no harm, where "doing harm" is defined as "performing some act A which leaves the individual worse off than he or she would have been if A had not been done." Note that, with this wording, the Harm principle is violated not only if I injure someone, but also if I prevent someone from getting a benefit which she would have otherwise received. So in the case of the Tuskeegee study, the researchers harmed their subjects if they prevented them from getting penicillin. Likewise, they harmed their subjects if they prevented them from obtaining information about the existence of penicillin. Did the researchers in the AZT studies harm their subjects in analogous ways? No one has charged that they intercepted benefits that were on the way to subjects, or that they injured them in the course of the research. So even if the Standard of Care argument is mistaken, the researchers still cannot be blamed for causing harm.

The Duty to Benefit

The AZT researchers did not harm their subjects. But it might be argued that they did not help them either, violating some moral principle to help those in need. But what exactly is this principle?

Certainly the principle cannot be that the researcher must help each subject as much as he or she could. This would require the researcher to assist the subject with all her problems, medical, financial, emotional, and social. It would require researchers to devote their entire personal fortunes and all their free time to the benefit of their subjects. This is asking too much; imposing this requirement would end all research.

Even at the medical level, it is not clear what is required by way of benefit. The criticized trials included studies of TB treatment among HIV-infected persons as well as the much discussed studies in prevention of vertical transmission of HIV. The critics argue that researchers conducting maternal transmission studies should have done more than they did to stop maternal transmission in their subjects. They also argue that the researchers conducting TB studies should have done more to stop TB in their subjects. But they do not argue that people doing TB studies should do more to treat maternal transmission, or that people doing maternal transmission studies should do more to treat TB.

These attitudes lead to implausible results. Suppose that there are four clinical studies running, D and E in x-town, F and G in y-town. In study D (HIV and maternal transmission), researchers treat half of the subjects for maternal transmission (the other half are on placebo) and provide all of the subjects, by way of ancillary care, with prophylactic treatment for TB. In study E (HIV and TB prevention), researchers provide half of the subjects with prophylaxis for TB (the other half are on placebo) and all of the subjects, by way of ancillary care, with AZT for maternal transmission problems. According to the critics, D and E are immoral, because of the placebo arms. In study F (HIV and maternal transmission), all the subjects get treatment for maternal transmission, but no one gets ancillary prophylaxis for TB. In study G (HIV and TB prevention),. all the subjects get prophylaxis for TB, but no one gets ancillary treatment for maternal transmission. According to the critics, F and G are morally exemplary, because there are no placebo arms. But the health care delivered to subjects in x-town is superior to the health care delivered subjects in y-town; 75% of the subjects in x-town get prophylaxis for TB and treatment for maternal transmission, while only 50% of subjects in y-town receive such care.

Morality demands that the fortunate help the unfortunate, but it leaves some leeway as to when, where, and how we give this help. Perhaps one of the occasions when people are not required to be in the helping mode is when they are engaged in clinical research that leaves them blind as to who needs help. But before we reach the conclusion that clinical researchers are uncharitable brutes exploiting convenient loopholes in the moral law, consider this. Every person entering into one of the disputed AZT studies obtained a benefit from doing so — a 50% chance of obtaining AZT. This is a real benefit because it is worth real money. (In a therapeutic setting with limited quantities of AZT, people would pay real dollars or real dinars for a lottery ticket providing a 50% chance of getting AZT.) Of course, if a person loses out in the AZT lottery, the lottery ticket becomes worthless, and likewise if a person is randomized to a placebo arm of an AZT trial, her 50% chance of getting AZT evaporates. But the fact that a benefit evaporates does not mean that it was not provided. To say that these clinical researchers provided no benefit to subjects on placebo would be like saying that a physician who initiates a therapy with a 50% chance of saving a patient's life has done nothing to help the patient, if in the end the patient dies.

It might be objected that all this philosophical talk about probabilities and benefits loses sight of the human tragedy at the heart of the problem. Here is a pregnant woman with HIV. I am a physician with a supply of AZT. If the woman gets AZT, this may prevent the birth of an HIV-infected child. This is a medical emergency: swift action is needed to prevent irreversible harm. But I don't give the woman AZT. I'm doing a study; my goal in life is to hit a confidence level of 95%. Have I lost my soul to science? If I encounter a drowning woman, don't I have an obligation to throw her a line, rather than study the drowning process?

There are, we rush to note, mitigating circumstances. If I don't give the woman AZT, she may well have a non-infected child; the odds are two-to-one that the baby will be fine. On the other hand, if I give the woman AZT, she may have an infected child anyway. All that AZT does is to reduce the odds. But if all I can possibly do is reduce the odds of harm, is it not morally open to me to select the means by which the odds are reduced? If I have a quantity of a drug which will reduce the chance of death in one person by 50%, am I not morally free to divide the dose in half, if by so doing I can reduce the chance of death in two people by 25%? And if all I can do now is reduce the chance that a woman will give birth to an infected child, is it not open to me to select a procedure which will reduce the chance of infection in a larger group of women, including women who will benefit when the trial is over? What moral principle says that this woman in immediate need has a right to help, but those women in future need have no such right?

These considerations are particularly relevant to the Helsinki-inspired suggestion that all subjects, or some subjects, in these trials should have received the standard Western long course of AZT, in which therapy is inaugurated as early as the 14th week of pregnancy. Since most women in the countries in question do not seek medical assistance until late in pregnancy, a trial involving the long course of AZT, with its daunting recruitment and compliance problems, would have been more time-consuming. A quick result demonstrating the efficacy of the short course at low cost clears the deck for the budgetary allocations and foreign aid appeals that may prevent more infections in the long run. The pregnant, infected woman in front of you is an emergency. The group, all of whom are pregnant, infected women, is also an emergency. This is not a choice between emergency and research. It is a choice between emergencies.

Voluntary and Informed Consent

The physician engaged in a research study seeks the good not of individual subjects, but the larger constituency of afflicted persons. Of course the individual subjects have rights, secured and expressed in the consent process. But there have been persistent assertions in the media that the consent process failed to legitimize the AZT studies because the consent given by subjects was not voluntary and not informed (29).

The argument that the consent for these studies was not voluntary hinges primarily on the consideration that subjects in the study were desperate. “At the time they explained this to me I asked myself the simple question of whether I had any choice. As long as there was a possibility to save my daughter, I had to try,” said one subject in the Ivory Coast trial (29). That the subjects in these studies were often desperate is beyond doubt. Their desperate condition necessitates special moral protection. It is, for example, a principle of both law and morals that persons cannot be held to contracts made from desperation. It would follow, then, that these subjects could not be held to any agreements made upon entering into the studies, a consideration guaranteed in any event by the rule of research ethics that every subject is free to withdraw without penalty at any time. Nor could researchers legitimately charge subjects for participation, but this too is forbidden by the existing canons of research ethics.

The crucial moral point is not whether desperation is present, but whether the presence of desperation signifies an absence of consent. If desperation invalidates consent, then every last-ditch cancer study, every study of refractory epilepsy, indeed, every study of a serious medical problem for which there is no treatment, would be immoral. This conclusion holds for studies in advanced countries as much as in developing ones. The sick are desperate in every country. Among the ethicists, there is no consensus that desperation invalidates consent. There is only agreement that coercion invalidates consent, and that is a different matter (30). Researchers coerce their subjects if they threaten them with harm for not participating. Thus it is possible for subjects to be desperate but not coerced, as well as coerced but not desperate. The mother from the Ivory Coast reports desperation, not coercion. I do not mean to suggest that bad external conditions are irrelevant to consent. Being in prison invalidates consent, even when threats are not made, and consent to a study of a disease would be invalid for subjects who were surreptitiously infected with that disease by the researchers. But these are not the sorts of situations surrounding these trials of AZT.

The question of whether or not consent to a given study is "informed" is a problem worldwide. The bottom line must be that subjects understand that their participation is voluntary, that they are participating in a research study, and that participation in a research study is not the same thing as getting the best possible medical treatment (especially for studies that involve randomization into placebo or sub-optimal treatment). There is every reason to believe that some research subjects do not grasp the difference between treatment and research. What I refuse to concede is that this problem is more acute in developing countries than in developed ones. Most accusations of racism in this debate have been bogus, but it is indeed racist to imply that Americans and Europeans have the intelligence to comprehend consent forms but that Asians, Africans, and Latin Americans do not.

A particular moral problem arises when an effort has been made to inform a subject, the subject remains uncomprehending, and participation is beneficial for the subject. An expectant mother in the Ivory Coast trial, handed a positive result for HIV, agrees on the spot to participate in a placebo-controlled trial (29) "because of the medical care they are promising me." This looks like uninformed consent. But if the woman is excluded from the trial, she loses her only chance of getting AZT. Can we suppose that if the woman had comprehended the notion of placebo and the possibility of non-treatment, she still would have participated in the trial? Rationality favors it, but on the other hand she might have thought it too much trouble in return for a mere 50% chance of getting AZT.

Conundrums like this prompt me to suggest that the moral standard for valid consent should not be the presence of information but the absence of deceit. If a research subject has false beliefs about the study, but these false beliefs have not been induced by the researchers (if, indeed, the researchers have made a reasonable effort to uproot these false beliefs), then the consent can still be valid because it is undeceived. If the researchers in the Ivory Coast study said things that induced a woman to believe that she would surely receive AZT, then her consent, resulting from this deception, was invalid. But if the Ivory Coast researchers tried to explain the notion of placebo and the woman persisted in believing that she would definitely get AZT, the consent is valid because it is undeceived, provided all other ethical requirements are met. In fact, some effort was made to explain the notion of placebo to this woman (29). Likewise, the efforts of researchers in Thailand to translate and explain the word "placebo" to their subjects show a thoughtful and concerted effort to inform (31). No one anywhere perpetrated a campaign of deception, in the high Tuskeegee style.

I suggest that the old requirement that consent should be voluntary and informed be replaced by a new requirement that consent should be uncoerced and undeceived. This is not a weakening of moral standards, but a focused attempt to capture what morally matters in the consent process. Coercion in research is morally wrong; deception in research is morally wrong. The consent process must rule them out. But the inability of subjects to comprehend the details of consent forms is not so much a moral issue as a fact of life. Likewise, the desperation of the sick is a fact of life. If we insist on scientifically literate, happy and undesperate subjects, we will only encourage contempt for the consent process, since such subjects will not be found and research will proceed anyway. For the ethicists and researchers who view the search for informed consent as a clumsy charade, contempt is what the process deserves. But for persons like myself, who defend trials with sub-optimal regimens, the consent process is essential: how can sub-optimal trial arms be legitimate unless subjects consent to their presence? The correct resolution of these dilemmas is not to junk consent (32) or to stop research, but to find the morally relevant form of consent and insist upon it.

Exploitation and Justice

Though all the trials in question proceeded with the consent and support of relevant national public health officials (33), in a number of cases the studies assumed a potentially disturbing form: white researchers/black subjects. The track record of white people among black populations is not good; locals have a right to fear the worst. The argument that these AZT trials "could not have been done in a Western country" gave the impression that white researchers were trolling worldwide for exploitable participants, pouncing on subjects where the regulatory forces were weakest. If so, the AZT trials would be morally comparable to the efforts of multinational corporations to find and exploit developing countries with weak environmental regulations or lax occupational safety requirements.

But the AZT trials could not be done in the West because they were tests of therapies not needed in the West. Comparative regulatory strength was not the issue. There is a generally accepted principle of international research ethics that trials in a country should focus on medical problems in that country (34). Since the problem of finding a short course treatment for maternal transmission of HIV was a problem specific to developing countries, the trials proceeded in appropriate locations with appropriate subjects.

So far, the majority of AIDS therapy trials have been in developed countries, with the majority of AIDS patients being in developing countries. The sacrifices of subjects in the AIDS trials in developed countries have been considerable, and the knowledge gained from Western trials benefits persons with AIDS in developing countries. Now it has been a guiding principle of research ethics for more than thirty years that the burdens of research should be equitably distributed among those populations that stand to benefit from the research (35). I will not suggest that populations at risk in developing countries have exploited the Western research subjects who have been overdosed or undertreated or otherwise suffered so that AIDS research could go forward. But I do think that the sacrifices of Western research subjects for more than two decades serve as a sufficient rebuttal to the misplaced charges of exploitation thrown at the sponsors of trials in developing countries in the mid-1990s. At worst, the sponsors of these trials could be called opportunistic: they saw an opportunity for research and they seized it. But this opportunism is not a special feature of research in poor countries. In medical research at large, every disease is an opportunity for grants, for work, and for a cure.

Ethics Charges and Research Progress

If I were a young clinician observing the charges of racism and exploitation thrown about in this controversy, I would be inclined to steer away from work on world public health problems rather than negotiate the ethics minefield laid down by contemporary moralists. No one is going to call you a moral monster if you devote yourself to acne problems in American kids. If I were director of research for a multinational drug company, I would learn from this controversy that it is better for the corporate image, and surely more profitable, to develop copycat versions of Viagra® than to take on malaria, TB, AIDS, giardiasis, shigellosis or any of the other diseases of the poor that make up the greater part of human suffering. There is indeed an ethics problem in this area: the misallocation of research funds away from the primary scourges of human life (36). But the charges leveled at the AZT trials can only make this problem worse.

The psychological impact of an ethics accusation is considerable, and only those who have lived through one know the stress of the experience. Those who conducted these trials have been through mental hell. Nevertheless, research goes forward and progress is made. The recent announcement of the effectiveness of oral miltefosine is a signal advance in treating visceral leishmaniasis, which afflicts 500,000 victims in developing countries each year (37). In the current climate, I can only hope that the researchers who brought in this result have their consent forms in order.

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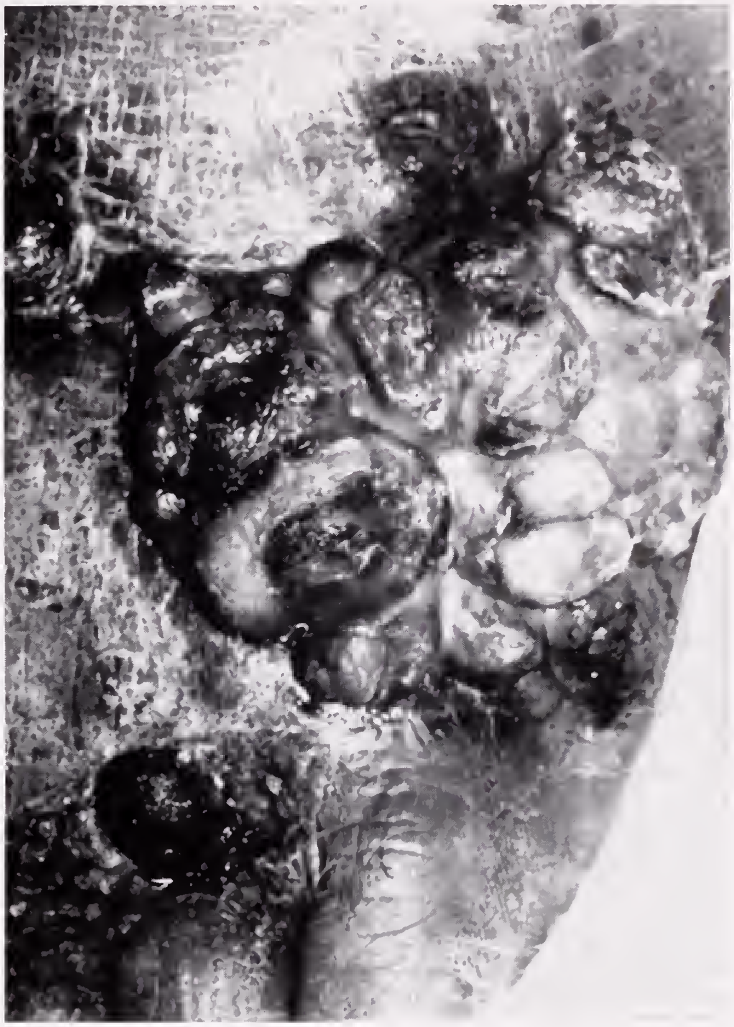
Dermatology Notes

AIDS-Related Kaposi's Sarcoma



ULCERATING, vegetating lesions of Kaposi's sarcoma are rarely seen now that effective retroviral therapy exists.

—Donald Rudikoff, M.D., and Mark G. Lebwohl, M.D.

The Key Extended Entry Program (KEEP):

A Methadone Treatment Program for Opiate-Dependent Inmates

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Abstract

The Key Extended Entry Program (KEEP) is the only known methadone treatment program for incarcerated opiate-dependent inmates in the United States. Initiated in 1987, KEEP performs approximately 18,000 detoxifications and 4,000 admissions for methadone treatment per year. Of those methadone treatment patients discharged to the community, mostly to outpatient KEEP programs, 74–80% report to their designated program. Recidivism rates reveal that 79% of KEEP patients were incarcerated again only once or twice during a recent 11-year period. Finally, KEEP data point to the importance of dedicating slots in the community for released inmates and maintaining them on sufficient blocking doses to eliminate the craving for heroin. About 6% of KEEP patients, some with mental illness, have a high incidence of recidivism.

Key Words: Methadone, correctional treatment, jail, discharge planning, recidivism.

Introduction

WITH A SIGNIFICANT INCREASE in the number of drug-related arrests in the New York Metropolitan area in 1987 (1), the Correctional Facility on Rikers Island experienced troubling overcrowding and unrest. In response, the Key Extended Entry Program (KEEP) was initiated through the cooperative efforts of the New York City Department of Correction and the New York Division of Substance Abuse Services. Conceived as both a narcotic treatment program and an AIDS prevention initiative, it remains the only known methadone pharmacotherapy program of its kind for incarcerated opiate-dependent inmates in the United States.

There are two components to the KEEP program. The first is the jail-based program at the NYC Rikers Island Correctional Facility, sometimes referred to as Pre-KEEP. The second component is the community-based KEEP programs that accept direct referrals from Rikers Island as well as walk-in admissions and referrals from other health, social service, and criminal justice agencies. The focus of this article will be on the KEEP services provided at Rikers Island and the linkages that have been made with the community-based KEEP programs.

Prior to the initiation of KEEP, many opiate-dependent inmates with minor offenses were released to the community before their detoxification was completed. Releasing such inmates in the throes of withdrawal nearly guaranteed a return to addiction, criminality and high-risk behaviors, including exposure to HIV, tuberculosis, and other infectious diseases. Offering inmates a choice of heroin detoxification or methadone treatment allowed for suitable inmates to make a transition from Rikers Island to community-based methadone treatment centers upon their release. KEEP's creation of dedicated

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slots for released inmates from Rikers Island has facilitated this transition for these otherwise difficult-to-place patients.

Patient Eligibility Criteria

Selection for the KEEP program depends on the medical and legal status of the patient. Candidates are selected from those patients placed, by medical staff, on one of two withdrawal protocols:

- Heroin withdrawal protocol – involves 12 days of tapering methadone
- Methadone withdrawal protocol – the tapering period is based on the community program dosage, i.e., a patient on 100 mg of methadone will receive a 39-day tapering protocol.

Staff from KEEP and the Department of Correction determine legal eligibility.

Legal Eligibility Determination

KEEP staff generate a list of potential candidates from the previous day's admissions who were placed by medical staff on a methadone detoxification protocol. This list is submitted to the Department of Correction for legal screening. The Inmate Identification System is used for patient verification.

Patient eligibility includes the following criteria:

- patients sentenced to less than one year of jail time
- patients detained in jail for legal charges that will not result in a jail sentence of more than one year, if found guilty
- patients who *plea bargain* their charges while detained (i.e., plead guilty to a lesser charge), whose sentence will result in less than a one-year jail term.

The following patients are not eligible for admission to the program:

- patients whose charges will result in a sentence of more than one year. Note: Those sentenced to a term greater than one year must be transferred from the New York City Correctional System into the New York State Correctional System, which does not currently provide methadone maintenance treatment.
- Patients who are detained for a violation of New York State Parole (e.g., patients who were on parole but were not compliant with the rules and regulations of parole).

Patients must comply with the rules and regulations of the KEEP program as well as the rules contained in the Inmate Rule Book. Violation of these rules may lead to termination from the KEEP/Detox Program. Patients terminated from the program receive an individualized detoxification schedule which is determined by the KEEP program medical director.

Admission

Patients are interviewed on admission to the KEEP program. This session includes an orientation to the program's services and rules. Educational material is presented to help the patient understand methadone treatment and general substance abuse treatment issues. AIDS education is also provided, aimed at reducing risk behaviors. Discharge planning begins with the admission interview.

Admission Procedure

The admission interview covers:

- an orientation to the KEEP program, informing the patient that the program is voluntary and that detoxification can be requested at any time. Other treatment options for opiate-dependence are also discussed with the patient.
- the provision of information about methadone to clarify any misconceptions that the patient may have. This education includes information on the benefit of increasing methadone dosing to achieve therapeutic levels.
- introductory information on transmission of disease and risk reduction behavior. Patients are informed that educational presentations will be ongoing during their participation in the KEEP program.

At the time of admission, the KEEP counselor completes a referral letter to a community based KEEP program. This letter is issued to the patient at the end of the admission interview. The KEEP counselor informs the patient of the location and offers travel directions to the selected community-based KEEP program.

The KEEP counselor determines the methadone dosage level according to the patient's detoxification status and confers with the physician on the medication order. The interaction of some medications with methadone (e.g., rifampin) may require the methadone dose to be adjusted. A patient from a community methadone maintenance treatment program is maintained on the dose prescribed by that program. This would include patients who enter KEEP on relatively high doses of methadone, i.e., 150–200 mg, when recommended by their community physician. Patients who were illicit heroin users and not in methadone treatment at the time of admission are encouraged to agree to a dosage level of 70 mg. If they do not agree, they will be maintained on 30 mg.

At admission, the KEEP counselor contacts the New York State Methadone Central Registry and the community-based KEEP program where the patient will receive aftercare. If the court or release date is known, this information is given to the community-based program.

Documentation

All patients admitted to the KEEP program participate in the completion of an individualized treatment plan. Treatment plans are reviewed and updated as needed but not less than every two months. A progress note is written for all patients at the time of admission to the KEEP program. The note contains the following information:

- Date, time and patient location at the time of admission.
- Statement that the patient has been accepted into the program.
- Statement that the rules and regulations of the program have been reviewed with the patient
- Patient's KEEP medication dosage, duration, and frequency of administration.
- If the patient is from a community-based methadone program, documentation is made of the name of the program and the previous medication dosage.

Progress notes are also placed in the chart when the patient's medications are renewed and when the treatment plan is updated.

Treatment Program

Medication Administration

Methadone is administered daily utilizing the Direct Observation Therapy (DOT) method. That is, a nurse and a correction officer directly observe the patient swallowing the methadone. Before leaving the area, each patient must also respond verbally to the correction officer to further insure ingestion of the medication. The diversion of methadone has been a remarkably minimal problem when utilizing this method.

Psychoeducation

Counselors meet regularly with KEEP patients to determine how they are tolerating their maintenance dose of methadone and to discuss treatment issues. Treatment, offered in both individual and group formats, combines the provision of information with discussion. In many cases, handouts highlighting some of the following points are made available:

- Methadone treatment is a medically supervised procedure in which a daily oral dose of a long-acting synthetic narcotic medication is received.
- Methadone is most effective when one is given a dose that "blocks" the effects of heroin and reduces craving for it.
- Methadone produces no significant side effects. It is a legal medication, made by licensed and approved pharmaceutical companies using high standards of quality control.
- Methadone does produce physical dependence, meaning that withdrawal symptoms and drug craving will be experienced if methadone treatment is stopped abruptly without a medically supervised detoxification program. It must be understood that there is a high risk for returning to heroin use if methadone treatment is stopped in an inappropriate way.
- Methadone can help you stop the use of street heroin, and lead to a more stable and productive lifestyle.
- Methadone is not a treatment for cocaine abuse or for abuse of other drugs or alcohol.

HIV Treatment Services

KEEP provides counseling on HIV prevention and risk reduction, case management, and intensive discharge planning services. Discharge planning includes making application for entitlement housing and referrals to residential health care facilities, the latter of which requires the provision of extensive medical documentation.

Relapse Prevention

KEEP provides relapse prevention services to a target group of patients who return to Rikers after a first treatment episode. Through individual and group counseling and peer feedback, recidivist patients are encouraged to identify triggers to relapse and to develop alternative methods of dealing with those triggers. Through ongoing psychoeducation and group support, patients are encouraged to adhere to their treatment plan.

Alternatives to Incarceration Services

KEEP also provides alternatives to incarceration (ATI) services by evaluating detained inmates for placement in drug-free residential therapeutic communities, residential methadone-to-abstinence programs, and outpatient ATI programs. Linkages developed with numerous criminal justice agencies have enabled KEEP staff to provide these services to those detained inmates whose needs would be better served by drug treatment than by incarceration.

Referrals to Other Treatment Services on Rikers Island

In 1998, the Therapeutic Community Services (TCS) program was initiated on Rikers Island. This program, funded by the Department of Correction, is run by St. Barnabas Hospital under the auspices of Health and Hospitals Corporation-Correctional Health Services. TCS is a drug-free program that offers treatment and discharge planning to patients within a modified therapeutic community environment. Patients who choose to withdraw from methadone are regularly referred to the TCS program. KEEP has also forged a strong working alliance with Mental Health Services, which provides counseling in all the buildings housing KEEP patients. This allows KEEP patients who have psychological problems and/or are on psychiatric medications to receive mental health treatment while maintaining their enrollment in KEEP.

Results

An analysis of Table 1 demonstrates a significant increase in the number of heroin withdrawal protocols after 1995, with a fairly consistent number of patients utilizing these protocols since 1996. MMTP withdrawal protocols increased steadily until 1998, but dropped in 1999, consistent with an overall decrease in the number of inmates admitted to Rikers Island in 1999. The number of patients undergoing observation prior to either opiate withdrawal or appropriate medication has been remarkably consistent over this 5-year period.

Table 2 indicates that the number of admissions to KEEP treatment services reached a record high in 1997, but has shown a slight decrease in the past two years, consistent with a decrease in the overall inmate census on Rikers Island. The reporting rate to aftercare has remained between 78–80%. The reporting rate of KEEP patients compares very favorably with those reported for any other population of patients (2).

Table 3 reveals the total number of discharges from the KEEP program during 1999. The data for male and female patients are grouped. The 78% rate of reporting to community-based treatment organizations (CBOs) is calculated from the number discharged to a CBO. During this period, the sentenced males were more likely to voluntarily withdraw from the KEEP program, while the detained males were more likely to be

TABLE 1
KEEP Detoxification Services (1995–1999)

Year	1995	1996	1997	1998	1999
Heroin Withdrawal	8,844	11,454	11,312	11,840	11,058
MMTP Withdrawal	5,786	6,030	6,385	6,548	6,062
Opiate Withdrawal Observation *	1,252	1,158	1,289	1,346	1,296
Totals	15,882	18,642	18,986	19,734	18,416

* Individual is assigned to observational period prior to a determination to withdraw drug or admit to an appropriate medication program.

TABLE 2

KEEP Methadone Treatment Services (1995–1999)

Year	1995	1996	1997	1998	1999
Admissions	3,802	3,940	4,373	4,331	3,929
Discharges to Community	2,903	3,205	3,631	3,433	3,177
Reported for Treatment	2,258	2,548	2,847	2,707	2,463
Reporting Rate (%)	78%	80%	78%	79%	78%
Average Daily Census	438	474	470	425	390

TABLE 3

KEEP Discharge Rates
Detained and Sentenced Males and Females
January 1 – December 30, 1999

	Detained Males	Sentenced Males	Sentenced and Detained Females	Totals
Total # of Discharges	1,131	1,550	1,216	3,897
# who voluntarily withdrew	42	104	22	168 (4%)
# terminated from program	107	13	40	160 (5%)
# transferred	353	39	0	392 (10%)
# discharged to CBO*	629	1,394	1,154	3,177 (80%)
# reported to CBO*	464 (74%)	1,078 (77%)	921 (80%)	2,463 (78%)

* Community Based Organization

terminated. A significant number of detained males were transferred, most of them into the KEEP program for sentenced males. Because all female inmates reside in the same building on Rikers Island, treatment is seamless for those enrolled in KEEP when they are transferred from detained to sentenced status. Overall, the data suggest that the female KEEP patients are slightly more likely to remain in KEEP while at Rikers and to report to their CBO upon discharge than are either the detained or sentenced men.

Table 4 examines the aftercare adherence of inmates who were not involved in substance abuse treatment prior to incarceration. It is evident that patients without prior connection to a program are much less likely to adhere to aftercare than are those previously involved in treatment. This argues that it is not just methadone dependence that predicts aftercare adherence, but also prior familiarity with treatment and/or a specific treatment program. Interestingly, patients discharged on higher doses of methadone are substantially more likely to report to a CBO than are those on lower doses. This supports the belief that patients must achieve a true "blocking dose" in order to remain in treatment and to eliminate the craving for heroin.

Table 5 demonstrates that nearly four-fifths of KEEP patients have been admitted to Rikers

TABLE 4

Aftercare Adherence of Patients Not in Treatment
Prior to the Rikers Admission (1998)

Methadone Dose at Time of Discharge from Rikers	# Patients Discharged	# Reported to CBO	% Reported to CBO
< 30 mg	1,273	664	52%*
≥ 30 mg	341	247	72%*
Totals	1,614	911	56%

* $p < 0.001$

TABLE 5
KEEP Recidivism Rates for 11 Years
January 1988 – December 1998

Frequency	Number of Patients Admitted (n)	Percentage of Patients Admitted %
1x	10,324	59
2x	3,426	20
3x	1,430	8
4x	734	4
5x	444	3
6x or more	1,112	6
Totals	17,470	100

Island only one or two times during a recent 11-year period. While overall recidivism rates are not available, the KEEP patients are demonstrating a remarkably low rate of recidivism, given their long history of drug involvement. These data suggest that KEEP may be playing a significant role in reducing jail recidivism in the majority of opiate-dependent individuals that it treats. This would need further study involving comparison groups. There remain a subgroup (6%) of difficult-to-treat patients, however, who are frequent recidivists (6 times or more) and who require specialized treatment.

Table 6 reveals that the number of methadone patients receiving HIV medication has been very consistent over this 5-year period, especially considering the slight decrease in the jail and the KEEP census in the past two years. By contrast, there has been a marked decrease in the use of tuberculosis-preventive medication and Directly Observed Therapy medication. Most striking is the sharp increase in the use of psychotropic medications by patients in KEEP. The data reveal that only 8% of the KEEP patients were on psychotropic medications in 1995 (# on psychotropics/average daily census) at any one time compared to 18% in 1999.

Discussion and Conclusions

KEEP has been in operation on Rikers Island for over 13 years now. While incarcerated, KEEP patients have been motivated to receive in-jail treatment and a community-based placement; they frequently report having difficulty negotiating the latter themselves. Anecdotally, the Department of Correction reports a decrease in the use of sick call because inmates are no longer forced into opiate withdrawal. Secondly, KEEP patients have been reported to be less of a management problem in jail because violation of the Inmate Rule Book results in the immediate removal of the patient from KEEP and, ultimately, a detoxification from methadone. Moreover, KEEP outpatient services, by facilitating the transition after release from jail, fosters overall compliance and aftercare.

KEEP offers the option of withdrawal from heroin or methadone, or maintenance on methadone during incarceration. Both options have been utilized by a substantial number of incarcerated patients over this time period. The majority of those who choose methadone treatment leave Rikers Island in good standing from the KEEP program and report to CBOs at a remarkably consistent 74–80% rate. Most of the CBOs are community-based KEEP programs that are designed to continue treatment on a more long-term basis. The data suggest that when inmates admitted to Rikers have not been in treatment prior to admission, their rates of aftercare are markedly lower. This argues for the need for patients to identify with a particular outpatient treatment setting in order to ease the transition from jail. The outpatient treatment center assumes responsibility for

TABLE 6
Average Number of Methadone Patients Receiving Other Medications per Day

Year	1995	1996	1997	1998	1999
HIV Medication	59	56	*	48	48
Tuberculosis Preventive Medication	24	14	*	10	6
Directly Observed Therapy Medication	10	5	*	4	2
Psychotropic Medication	34	34	*	51	72
Average Daily Census	438	474	470	425	390

* Data not available

continuing to administer sufficient blocking doses of methadone in order to eliminate the heroin craving and to maintain the patient in treatment. This appears to be crucial. Remarkably, nearly 80% of KEEP patients have been admitted to Rikers Island only once or twice during a recent 11-year period. There do remain, however, a small cluster of patients who are frequent recidivists. Some of these patients, i.e. those with multiple problems, need more comprehensive services. Others, who are more intractable, are often kept in treatment in the interest of reducing their risk to themselves and to the public at large.

Maintenance on less than 30 mg of methadone may prove to be insufficient treatment for the majority of opiate-dependent individuals. This finding is supported by previous research (3), which found that KEEP patients accepting a high dose (≥ 60 mg) were significantly less likely to be reincarcerated than were those accepting a low dose (≤ 30 mg). While a fixed higher dose correlated with reduced recidivism, these authors recommended routine methadone plasma level monitoring to adjust doses to achieve "blocking dose plasma levels." These observations suggest that a sufficient methadone dosing practice (≥60 mg daily.) is essential to program effectiveness.

The more than twofold increase in use of psychotropic medications, as indicated in Table 6, emphasizes the need for increased mental health involvement for this population of patients. The reason for this increased use of psychotropic medications is not known.

Health care administrators and personnel have changed their opinions about substance abuse treatment in the last twenty years. Concerns that methadone treatment is merely substituting one drug for another have been replaced with the belief that many individuals receiving methadone treatment lead productive lives and engage in less criminal activity and fewer health risk behaviors. In addition, viewing substance abuse treatment as a process in which addicted individuals move through predictable stages of readiness for change (4) offers more hope to both the patient and the practitioner. With that hope, patients are more likely to remain in treatment. While health risk behaviors are difficult to assess, the KEEP data would suggest that this program has been effective both in maintaining patients in treatment and in reducing criminal behavior. KEEP will continue to refine its methods to serve those patients who present with special needs.

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The Key Extended Entry Program (KEEP):

From the Community Side of the Bridge

Bryan M. Fallon, Ph.D.

Abstract

The Key Extended Entry Program (KEEP) engages heroin addicts who were not in treatment at the time of arrest, in community-based substance abuse treatment upon release from the criminal justice system. KEEP also serves as a transitional program providing short-term treatment to street heroin addicts with brief addiction histories and little or no experience in treatment. The program goals include reductions in heroin use, HIV transmission, and recidivism. This paper describes KEEP at the Narcotics Rehabilitation Center (NRC) of The Mount Sinai Hospital, in terms of admission criteria and procedures, staffing, hours of operation, and program services. Furthermore, the paper presents a review of the literature evaluating the NRC KEEP in terms of its success in retaining patients, transferring them to long-term treatment; and reducing heroin and cocaine use, some HIV-risk behaviors, and certain kinds of criminal offenses. Recommendations are made for future program development.

Key Words: Methadone treatment, KEEP, heroin addiction, opioid dependence, substance abuse treatment, criminal justice.

Heroin addiction has long been associated with criminal activity, multiple episodes of incarceration, and social and medical problems. There clearly continues to be a public health need to intervene and engage this population in recovery. Yet only a small percentage of addicts are ever involved in treatment programs (1). To address this situation, the Key Extended Entry Program (KEEP) was developed in 1987, through the collaboration of the New York State Office of Alcoholism and Substance Abuse Services (OASAS), Montefiore Medical Center, and the New York City Department of Corrections at Rikers Island. This program was designed to assist heroin-addicted individuals who are not enrolled in treatment at the time of arrest, to become stabilized on methadone while incarcerated, and then to refer them to community-based treatment programs upon release.

The service mandate of KEEP also involves providing treatment to non-incarcerated, heroin-addicted individuals who may have a short history of dependence or have little or no treatment history. In addition, individuals are offered the opportunity for detoxification and for ongoing assessment of needs with subsequent referral to the appropriate type of treatment (from pharmacotherapeutic through drug-free to self-help).

KEEP aims to engage and maintain people in treatment, with the goals of: (a) decreasing heroin addiction; (b) diminishing risk of exposure to transmission of HIV; and (c) reducing recidivism. The purpose of the present paper is to describe the operation of KEEP from the community-based treatment perspective of The Mount Sinai Hospital's Narcotics Rehabilitation Center (NRC), and to review representative research directed toward assessing the efficacy of the KEEP model.

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KEEP at the Narcotics Rehabilitation Center

The NRC KEEP is licensed and funded through the New York State OASAS for a census of 75 patients. The medication hours are from 3:30 PM to 5:00 PM, Monday through Friday, and 8:30 AM to 11:30 AM on Saturday. The staff includes an intake worker, a registrar, a physician, a pharmacist, three methadone counselors, one social worker, a security officer, a receptionist, and several clerks; they are overseen by the KEEP director, a psychologist. Most staff are employed on a part-time basis.

There are essentially two routes for patients to enter NRC KEEP. In one, addicts are referred directly from Rikers Island. In the other, addicts walk in after having been referred by a needle exchange program by another department within The Mount Sinai Hospital, or by friends or family members.

Admission Criteria: Rikers referrals are considered the highest priority and are admitted directly to the program. If medication was taken at Rikers prior to release and no longer than three days previous to being seen in the program, then a toxicology screen will not be required for same-day admission and medication. Any other patient referred to the program must meet the criteria given in Table 1.

Admission Procedures: The staff at Rikers contacts the KEEP director and provides referrals to the program. Key identifying information is provided, along with the methadone dose and probable release date. Upon arrival at the NRC, the patient presents a letter of introduction from KEEP at Rikers. The intake worker confirms the last date and dose of medication. If the patient is a re-admission, the intake worker reviews the patient's old chart to assess eligibility for re-admission, and addresses any concerns with the KEEP Director. If the applicant does not qualify for re-admission, he or she may receive courtesy medication and be referred to another program.

TABLE 1
KEEP Admission Criteria

Current opioid dependence, which must be validated by positive urine toxicology

No more than 18 months of prior treatment in a maintenance program for narcotics

At least 18 years old

Residence in New York State

No need for immediate psychiatric hospitalization

Except for the Rikers referrals, the KEEP director screens all applicants to the program for eligibility. If the patient meets the admission criteria, verification of identity and a urine specimen for confirmation of recent opiate use are obtained.

Prior to formal admission, each patient is seen by the physician or nurse practitioner who: (a) conducts a physical examination; (b) documents opiate dependence; (c) obtains urine and blood specimens; (d) performs Tuberculin Purified Protein Derivative (PPD) tests and orders chest X-rays as medically indicated; (e) presents and discusses the two options, either levo-alpha- acetylmethadol (LAAM) or methadone; and (f) writes a prescription for the appropriate dose of maintenance medication.

The intake worker performs a range of tasks that include: (a) communicating directly with the statistical clerk and registrar to ensure that patients sign all the necessary information releases, consent forms, treatment waivers, and contracts; (b) providing the patient with information regarding medication hours, clinic rules and expectations, patient rights, and health care proxy prior to admission; (c) registering the patient with the Central Registry to guard against enrollment in more than one methadone program; and (d) serving as a liaison between the primary counselor and the medical department during admission.

Medication: For the past 1 1/2 years, patients have been offered the option of being treated with either methadone or LAAM. Patients are generally more familiar with methadone, since they have heard others talk about their experiences in methadone treatment or have used street methadone themselves. Based on familiarity alone, some patients prefer to receive methadone. These patients are willing and able to come to the clinic 6 days per week for their medication and receive a take-home bottle for Sunday. However, some patients are very much attracted to the convenience of LAAM's 3-day pick-up schedule. They may have jobs or childcare responsibilities that make it difficult to get to the clinic every day. The patients are informed of the advantages and disadvantages of each option, and make an informed choice. LAAM is not recommended for patients with severe liver or kidney disease, or severe alcohol problems; it is not prescribed for pregnant or breast-feeding women. Currently about 20% of the KEEP patients are taking LAAM; all of them are closely monitored to ensure build-up to effective dose levels and rapid response to any side effects.

Individual Counseling: Toward the end of the intake process, the patient is assigned to a counselor, the patient's primary contact and advocate, who obtains a psychosocial history (see Table 2). The counselor's main goal is to engage the patient in the treatment process by: (a) performing comprehensive needs assessment; (b) orienting the patient to some of the treatment procedures; and (c) conveying an understanding of the recovery process. In addition to orienting patients to the program rules and regulations, the counselor collaborates with patients to form a treatment plan for the next thirty days and meets with them at least weekly. Some patients seek more involvement than others. Counselors will provide referrals to shelters and food programs in addition to medical, psychiatric, and vocational services, on an as needed basis.

Each patient learns to submit random weekly urine specimens to monitor opiate and other drug use as part of assessing progress in treatment. The pattern of results can be used to identify the need for referral to additional or alternative substance abuse services (e.g., inpatient alcohol or cocaine detoxification).

TABLE 2
Psychosocial History

Age, race, place of birth, and current living situation
Source of referral
Drug history and treatment experience
Family history
Educational history
Vocational history
Source of financial support
Criminal justice history and current legal status
Medical history
Mental health history
Current mental status
Spiritual orientation
Patient's motivation for change and treatment goals, strengths and weaknesses
Formulation of initial treatment plan

Based upon the monthly treatment plan review, disposition planning begins no later than the third month of treatment. By this time, the patient has had some time to stabilize on methadone or LAAM, and to tend to other life issues. The counselor works with the patient to establish a plan for services following the sixth month in KEEP. The patient may request to be tapered off the medication, referred to an alternative type of program, or transferred to a maintenance program. The counselor ensures that a discharge plan is in place by the treatment plan review at the fifth month, and prepares the patient for the steps to be taken to optimize the likelihood of following through with the plan. All individual treatment and discharge plans are discussed with the KEEP director, and in weekly staff case conference meetings.

Ancillary Services

(a) **Concrete Services:** Patients are admitted to the program who do not have Medicaid or any gainful employment. Those coming directly from Rikers Island may have lost all their forms of identification, and have no home or financial support. Our counseling staff will provide referrals to the shelter system, and to food and clothing provisions. A benefits coordinator assists the patients in preparing the necessary and appropriate documents for the Medicaid and public assistance application process. Where appropriate, counselors will advocate for patients with the social service organizations.

(b) **Medical Services:** Apart from the standard services provided during the admission process, patients can choose to have their primary care services provided in the clinic. This is an important feature of the service at the NRC, because the availability of medical staff at the clinic increases the chances that the patient will seek evaluation and treatment. If the problem cannot be managed in the clinic, the patient is referred out to the appropriate facility.

(c) **Obstetrical and Gynecological Services:** Female patients can avail themselves of routine obstetrical care, gynecological care for illness, birth control methods, periodic check-ups, and follow-up on prenatal care.

(d) **Psychiatric Services:** A psychiatrist is available on a part-time basis to provide consultation, evaluation, medication, and referral. The staff social worker is usually assigned any patients that have co-morbid psychiatric problems.

(e) **Health Education:** All KEEP patients are offered the opportunity for HIV testing with pre- and post-counseling, education about practices for reduction of HIV and hepatitis C virus (HCV) transmission, referral for special services (e.g., Division of Aids Services [DAS], legal advice, linkage to HIV/AIDS treatment services).

(f) **Vocational Services:** KEEP patients have a diverse range of employment experiences and skills. A few are gainfully employed on admission and throughout treatment, some have worked for years off the books, and many have very little work experience. Patients are referred to the vocational rehabilitation counselor for prevocational assessment and counseling when the patient is ready and willing to pursue education, training, or employment.

Program Expectations

One of the primary goals of KEEP is to engage people in the treatment process, which requires that they be treated respectfully. Patients must learn the clinical and programmatic policies and procedures that frame the treatment experience as well as the importance of attending the clinic regularly to receive the medication, including the return of Sunday take-home bottles. Missing medication or failing to return bottles on a consistent basis raises a flag, which is addressed by the counselor. The clinical nurse manager reviews patients' attendance and bottle return each month, and generates warning notices for those who miss or fail to return bottles frequently within that period. If the trend continues during the next month, the patient receives a probation notice. Further misses, which are evaluated by the treatment team, may represent a reluctance or inability to comply with treatment expectations, and may merit administrative detoxification and/or referral to an alternative type of treatment.

We believe that an important part of recovery is assuming responsibility for one's own health. As in most other treatment settings, all patients are expected to make an effort to pay for services either through Medicaid or fees. Each patient admitted without a Medicaid number has thirty days from date of admission to apply. The patient is admitted to the program with the knowledge of this expectation. If after 30 days, the patient has not taken any steps to initiate the Medicaid application process, a probation notice is issued which indicates that this process must be completed within the next 30 days, at which time an administrative taper will be initiated. Alternatively, legitimate employment status must be verified by a pay stub within thirty days, so that a fee can be assessed. Failure to meet these requirements will result in discharge from treatment. Counselors work closely with patients to assist and encourage compliance.

Program Evaluation

After a brief description of the population served at the NRC, studies of KEEP are reviewed in terms of the following dimensions: treatment retention, heroin use, cocaine use, HIV transmission, criminal arrests, and treatment disposition.

Population Description: The population treated at the NRC KEEP is mostly male (81%), has an average age of 38 years, is Latino (40%) and African-American (40%), has never married (62%), has dropped out of school prior to completing high school (44%), is unemployed (92%), has a legal history on admission (95%), and is living in a home (72%) (2, and personal communication - Diab ME et al.). In contrast to earlier high rates of injection drug use (3, 4), more recently about one-half of the population use heroin intravenously or subcutaneously and one-half prefer the intranasal route. There have been no significant demographic differences found between Rikers referrals and walk-ins.

Retention: Several studies have examined retention levels in KEEP. In an initial evaluation of pre-KEEP at Rikers Island in 1987 (3), of the 1,146 admissions discharged to community-based methadone programs, 69% reported for and were accepted into treatment. In 1993, Magura, Rosenblum, Lewis, and Joseph (4) assessed the effectiveness of KEEP at Rikers on several dimensions including retention. The researchers compared 195 inmates admitted to KEEP who were not enrolled in methadone at the time of arrest with 54 inmates who were undergoing heroin detoxification. The latter group served as a control group. Upon release, 85% of KEEP participants vs. 37% of controls had applied for drug abuse treatment, both predominantly for methadone treatment. At the time of 6-month follow-up interviews, 27% of KEEP subjects and 9% of controls were enrolled in a drug treatment program, including methadone.

Focusing more specifically on the NRC population, Diab et al. (personal communication) investigated treatment retention, drug use, and discharge disposition for KEEP admissions, comparing Rikers referrals (n = 42) with walk-ins (n = 37). This study identified a high rate of retention for this population in the 6-month program. About 50% of the sample remained in treatment after 5 months. The mean total time in treatment for the Rikers Island group was 20.4 weeks, and 19.9 weeks for the walk-in group.

In contrast, an unpublished investigation by Rosenblum and Magura (personal communication) tracked 488 successive NRC KEEP admissions, from 1-1-91 through 3-31-95, through 24 weeks of treatment. They found that at the start of the fourth month of treatment about one-third (34%) of KEEP admissions were still in the program. This number had dropped to 21% retained in the program by the start of the fifth month. Thus, it appears that at least 80% of patients exit treatment before making the transition to long-term maintenance treatment. This finding highlights the need to improve treatment engagement and retention.

Bradbury (2) investigated a sample of 86 patients enrolled in KEEP to identify the concrete aspects of treatment that improved retention. Patients were compared on a variety of demographic factors at admission and discharge to assess whether changes in status were related to treatment retention. The best predictor of treatment retention was Medicaid status. More specifically, patients who were admitted to the program without Medicaid and still did not have Medicaid at discharge remained in the program for an average of 42 days, and tended to be incarcerated or lost to contact. Patients who had their Medicaid at admission and at discharge lasted an average of 95 days in the program. One-third of this group eventually transferred into long-term treatment, but one-third was lost to contact. However, the greatest retention was for those patients who came into the program without Medicaid but had received it by the end of treatment (an average of 166 days). Additionally, a significant correlation was found between homelessness and treatment retention; those patients who were homeless were more likely to drop out of treatment. Bradbury makes the point that treatment success is mediated through treatment retention, which is enhanced by advocacy in meeting the concrete needs of the patient.

Heroin Use: Magura et al. (4) found that about 90% of KEEP participants reported daily heroin use prior to arrest. The study showed that relapse to drug use is quite high among inmates released from Rikers. Eighty-eight percent of KEEP participants and 85% of controls (heroin detoxification) reported returning to heroin and/or cocaine use after release from Rikers. At 6-month follow-up, this was reduced to about 50% of KEEP participants reporting daily heroin use. This estimate was supported by Rosenblum and Magura (personal communication), who followed KEEP admissions through treatment at the NRC from 1991 to 1995 and found that the percentage of urines positive for opiates ranged from 55–61% across the 24 weeks of treatment. These estimates were given further support by Diab et al. (personal communication), who also found that opiate use rate was high (62%) throughout treatment. It seems that heroin use remains stable for many patients during the six months of treatment in KEEP. Therefore, for many of these patients, six months is not a sufficient amount of time to change substance using habits.

Cocaine Use: One of the consistently significant findings is the high rate of cocaine use in the KEEP population. Rosenblum and Magura (personal communication), who followed KEEP admissions through treatment at the NRC from 1991 to 1995, found that the percentage of urines positive for cocaine ranged from 62–71% across the 24 weeks of treatment. These estimates were given further support by Diab et al. (personal communication), who also found that cocaine use rates were high throughout treatment. With further analysis, these researchers found that the patients who had been referred from Rikers Island did have a higher proportion of positive cocaine urine toxicologies than the walk-in patients (81% vs. 45%).

Opiate agonist therapy is clearly not designed to directly address cocaine abuse. Nor are methadone maintenance programs particularly staffed to adequately treat secondary drug use. The usual treatment is referral for inpatient cocaine detoxification, which has been found to be ineffective in establishing abstinence (5). We investigated the efficacy of providing outpatient cognitive-behavioral therapy to treat cocaine use among patients on methadone maintenance at the NRC. The model has been described elsewhere (6). Recently published results by Rosenblum et al. (7) showed that patients in both high and low intensity cocaine treatment groups had significant and equivalent declines in proportion of urines positive for cocaine at the 6-month and 15-month follow-up points (from 0.72 at baseline to 0.58 and 0.56, respectively). The mean number of days using cocaine in the past 30 days (by self-report) showed a similar decline from 18.6 days of use at baseline to 9.9 and 11.2 days at 6- and 15-month follow-ups, respectively. Frequency of drug-injection and percent of injectors also declined at follow-up, e.g., from 40% using needles at baseline to 23% at 15-month follow-up. One key finding was that the high intensity treatment group did not show a greater overall decline in cocaine use than the low intensity treatment group. Completing either treatment was associated with lower proportion of cocaine positive urines at follow-up. However, baseline cocaine severity interacted with treatment intensity such that subjects using large amounts of cocaine (daily or near-daily users) were more likely to reduce their cocaine use if they were exposed to high intensity treatment. Those who had a less severe cocaine problem were more responsive to low intensity treatment. This observation suggests that patients should be matched to the appropriate level of treatment for maximal effectiveness in cocaine treatment, for patients on methadone.

Magura (personal communication) has applied this research model to NRC KEEP in an ongoing National Institute of Drug Abuse (NIDA)-funded study. These investigators have identified cocaine-using methadone patients at admission and offered them either regular methadone treatment or enhanced (individual and group) treatment with a cognitive-behavioral model targeting cocaine use. The treatment emphasized the importance of engaging patients and rewarding them for participation and progress in treatment. Patients were given financial incentives for completing concrete tasks that advanced them toward their treatment goals (e.g., attending therapy sessions, following up with medical/psychiatric appointments and/or public assistance/ Medicaid appointments). The results, which have not yet been published, should have strong implications for treating the problem of cocaine use among patients receiving opiate agonist therapy.

HIV Transmission: In terms of HIV transmission, Joseph et al. (3) noted that 78% of Rikers KEEP participants reported needle sharing prior to arrest, and 91% reported sharing cookers. Magura et al. (4) noted that baseline rate of injection drug use for this population prior to arrest was about 70%, and this rate dropped to 44% at 6-month follow-up for KEEP participants. Lower frequency of drug injection at follow-up was associated with remaining in treatment.

Arrests: Magura et al. (4), who assessed the effectiveness of KEEP at Rikers, found a consistently significant reduction in theft and illegal income, in association with drug treatment at 6-month follow-up. In terms of patients enrolled at NRC KEEP, Diab et al. (personal communication) found that for 6 months prior to discharge, the mean number of days incarcerated for the Rikers Island group was 3.0 and for the non-Rikers Island group was 0.59 days. The mean number of arrests for the 6 months prior to discharge was 0.73 for the Rikers Island group and significantly less, at 0.11 per person, for the non-Rikers Island group. Bradbury (2), in his assessment of NRC KEEP, found that 100% of the patients who were referred from Rikers Island without Medicaid and who then obtained Medicaid while in treatment, were not re-arrested during the six months in KEEP, whereas 38% of the remainder of Rikers referrals were discharged due to incarceration. This finding lends support to Magura et al. (4), who found that retention in KEEP leads to decreases in criminality. Participation in KEEP clearly does not eradicate involvement in criminal activities, but it is associated with a decrease in recidivism.

Treatment Disposition: Bradbury (2) noted that about 29% of NRC KEEP patients transferred into long-term treatment. More specifically, he found that treatment discharge disposition was a function of how well patients responded to the assistance in acquiring Medicaid. Most of the patients (81%) who had come to the program without Medicaid but had successfully obtained it, remained in the program longer and then transferred into the long-term maintenance program. Patients who were admitted to NRC KEEP without Medicaid and did not obtain it during treatment were more likely to drop out (62%) or be re-incarcerated (23%). Interestingly, patients who began treatment with Medicaid were equally likely to either transfer to Methadone Maintenance Treatment Program (MMTP) (33%) or drop out (37%). Diab et al. (personal communication) found that 53% of the overall sample continued treatment after completing KEEP. For both of these studies, there were no significant differences between Rikers referrals and walk-ins in terms of treatment disposition.

While this number is high compared to more conservative estimates of 20% (3, 4), KEEP has been modestly successful in introducing patients to long-term methadone maintenance treatment.

Summary

The KEEP population is a challenging group of people who often present with multiple impairments. They may recently have been released from jail, may be homeless, lack any identification or entitlements, have little or no sources of social support, may have medical or psychiatric complaints, and have severe opiate and cocaine dependence. Living on the edge or outside of regular work and social roles can make it very difficult for these patients to engage in the treatment process with all of its expectations, demands, and rules.

KEEP has demonstrated some success in reducing heroin use. However, some patients continue to use heroin throughout treatment. We need to assess the adequacy of methadone dose levels and the impact of LAAM on urine toxicology results. Cocaine use is quite widespread among KEEP patients. We must re-evaluate the efficacy of our interventions for treating this problem. For patients who remain in treatment, there is a reduction in injection drug use, which probably reduces the rate of HIV and HCV transmission. We need to identify HIV and HCV prevalence rates in the KEEP population, clarify our intervention and assess its impact. Treatment participation is also associated with reduced criminal activity in this population. Nonetheless, many patients continue to be involved in criminal activities and return to Rikers Island.

At best one-half and at worst one-quarter of our admissions complete treatment and transfer to long-term methadone maintenance or alternative programs. Thus, many individuals introduced to treatment remain in the throes of an addictive lifestyle while others do make the transition to treatment. Many who drop out are lost to follow-up, or they are re-incarcerated and do not return to treatment. The factors that underlie treatment dropout should be assessed and the program developed to enhance retention. We plan to evaluate whether the use of LAAM, with its less inconvenient schedule, contributes to greater treatment retention. Stabilizing on methadone dose and receiving help with concrete services improves the chances that some of these patients will decide to continue on methadone maintenance treatment and avoid re-arrest.

Even though KEEP was designed as a long-term detoxification program, few of our patients actually go through a planned detoxification process. If they decide to discontinue methadone, they usually walk away. There are not many success stories.

Finally, with the recent governmental emphasis on welfare-to-work, which insists that persons receiving public assistance abstain from any drug use and be ready to work, vocational rehabilitation services have assumed renewed significance. The impact of KEEP in terms of preparing people for employment has yet to be adequately assessed.

Nonetheless, despite its very limited success in rehabilitating heroin users, KEEP has proven to be extremely beneficial to some in allowing them a significant change in lifestyle.

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Integrating the Methadone Patient in the Traditional Addiction Inpatient Rehabilitation Program — Problems and Solutions

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Abstract

Physicians have reported alcoholism and opioid addiction as co-morbid conditions since the 19th century. From the inception of methadone maintenance treatment, heroin addicts with serious alcohol conditions have enrolled in methadone maintenance programs.

Programs that treat alcoholism, including the traditional addiction inpatient rehabilitation programs of the Addiction Treatment Centers (ATCs) operated by New York State, have based their treatment regimen on 12-step abstinence models. Methadone maintenance was considered antithetical to this philosophy. It was regarded as simply substituting one drug for another and not a legitimate treatment for opiate dependence. Therefore, methadone patients were often not accepted into alcohol treatment programs, since they were perceived as active addicts taking a mood-altering drug.

Alcohol-related conditions among methadone patients are major causes of liver disease and death, and behavior problems associated with excessive drinking are major reasons for discharging patients. To address these issues and the lack of treatment facilities, the administration of the New York State Office of Alcoholism and Substance Abuse Services (OASAS), which licenses both methadone programs and the ATCs in New York State, realized that many of the methadone patients with alcohol problems are in need of the services provided at the ATCs. They instituted, therefore, a rigorous educational effort for the medical and counseling staffs of the ATCs, designed to integrate methadone treatment into the ATC treatment framework.

Eighty percent of the 220 methadone patients who entered the ATCs in a demonstration project during the 1997/1998 state fiscal year have been compliant with the treatment regimen. These results have led to acceptance of methadone patients into the ATCs.

Key Words: Alcoholism, opiate addiction, methadone maintenance treatment, 12-step programs, inpatient rehabilitation, staff attitudes.

Introduction

Physicians have long been aware that alcoholism and narcotics addiction often coexist. According to Green and Jaffe (1), physicians have reported the excessive use of alcohol by narcotic addicts since the late 19th century. Terry and Pellens (2) and Courtwright (3) indicate that iatrogenic addiction was common in the 19th century, and that the administration of narcotics to reduce or "cure" alcoholism was a factor in the development of opioid addiction.

Kolb (4), in a U.S. Public Health Service study implemented in the 1920s, reports that 39% of the 230 addicts surveyed nationwide were heavy users of alcohol prior to and/or interchangeably with their addiction to narcotics. Pescor (5) reported similar findings a decade later: 37.4% of the 1,036 narcotic addicts admitted in 1936 and 1937 to the U.S. Public Health Hospital in Lexington, Kentucky reported having had serious problems with alcoholism prior to their addictions to and during periods of abstinence from narcotics.

With the establishment of methadone maintenance treatment (MMT) in the late 1960s and early 1970s, alcoholism was recognized as a serious health problem among methadone patients. Kreek (6, 7) found, in a prospective study, that at admission to MMT, 20% of 214 patients had serious alcohol problems and that health problems related to alcoholism were major causes of liver disease. In contrast, the estimated prevalence of alcohol abuse, and abuse and dependence problems among all adults over 18 years of age in the United States, is 7.41% (8).

In a study of outcomes of methadone treatment in the 1970s, Joseph and Appel (9) reported the following:

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- twenty-four percent (24%) of 1,428 randomly selected patients had serious alcohol problems;
- alcohol problems were the major factor in 26% of the 934 discharges from treatment;
- alcohol-related illnesses (e.g., cirrhosis) were the major causes of death for patients in treatment;
- alcohol-related illnesses were the second major cause of death, following narcotic overdose, for patients who left treatment;
- survival rates over a ten-year period were lower for patients who were considered alcoholic than for non-alcoholic patients (67% vs.87%); and
- programs for the treatment of alcoholism refused to accept methadone patients with alcohol abuse, and Alcoholics Anonymous did not admit methadone patients into its program.

Despite its approved use in the treatment of narcotic addiction in 1972 by the United States Food and Drug Administration (10) and favorable reviews as the most effective treatment for heroin addiction by the Institute of Medicine and the National Institute of Health, methadone maintenance remains a controversial approach among chemical dependence treatment professionals, public officials, policymakers, and the medical profession. There are those who believe that methadone maintenance is nothing more than a recognized substitute for opiate addiction and that it provides no clinical or rehabilitative benefit (11). In addition, the use of a maintenance medication for addiction appears to conflict with the philosophy of complete and total abstinence (11). Patients with a diagnosis of opiate dependence who are receiving MMT are often stigmatized; they have long been excluded from fully participating in AA meetings, and denied admission and treatment in traditional addiction and chemical dependence programs. Within the chemical dependence treatment system in New York State, the inpatient rehabilitation program was particularly resistant to providing medical and clinical addiction treatment to patients who were opiate dependent and maintained on methadone, while also addicted to alcohol and/or other drugs.

To more appropriately serve this special population, in 1996 the New York State Office of Alcoholism and Substance Abuse Services developed a pilot program to treat methadone-maintained patients with alcohol problems in their inpatient addiction-treatment system. In 1997, 220 patients with alcohol problems were recruited from methadone maintenance programs to enter the Addiction Treatment Centers (ATCs).

Patient Profile

The profile of the methadone-maintained patient is similar to that of the patient traditionally found in the inpatient alcohol rehabilitation program. The presentation is one of a polysubstance user of alcohol, heroin, cocaine, crack, or cannabis with mental health problems and social problems such as transient housing, homelessness and criminal activity. Also, patients present serious medical problems, including liver disease, heart disease, tuberculosis, hepatitis and HIV. Mental health diagnoses are frequently encountered. For example, high rates of depression with prevalence rates approaching 17% have been reported for methadone-maintained patients (12, 13). However, in the population of methadone-maintained patients treated in the ATCs, depression was seen in 24% and anxiety disorders in 20%. In addition to emotional disorders, serious social problems affecting the patients included homelessness, alienated families, criminal behaviors, unemployment, and financial problems.

Despite these problems, methadone-maintained patients who are admitted into the ATCs do exceptionally well in treatment, with 80% of the 220 admissions in the pilot study referred to above completing the goals of their treatment plan and successfully returning to their outpatient methadone treatment programs after discharge. However, the patients who are selected by a methadone treatment program for referral to an ATC are probably among the most motivated and therefore are most likely to succeed. The ongoing support that is offered through the referring methadone treatment program contributes to their clinical success.

Changing the Organizational Culture

Within the standard addiction inpatient rehabilitation program, treatment of methadone-maintained patients will only be successful if staff attitudes and expectations are addressed. Long-held misconceptions and biases by staff about methadone, patients on methadone maintenance, and MMT itself, have to be changed in order for the methadone-maintained patient to be integrated into the traditional programs of the ATCs. As described by Gordis (11), a philosophy existed in the ATCs that supported the mistaken notion that methadone, when used as a maintenance medication, was a mood-altering drug and a substitute narcotic prescribed for the purpose of reducing criminal drug-seeking behavior. Methadone was not perceived as a legitimate medication for opioid addiction. Therefore, patients maintained on methadone were often treated as unmotivated and unworthy of clinical intervention, and their treatment was perceived as solely ingesting the "drug." To offset misinformation and bias against methadone by the staffs of the ATCs, OASAS instituted an educational program about the proven efficacy of methadone as a legitimate medication to treat addiction.

In order to ensure that methadone patients in the ATCs have the maximum opportunity for success, methadone programs had to expand the number and types of treatment interventions they provide, including such services as bio-psychosocial assessments, level of care determinations, and a full diagnostic work-up. The referring methadone clinic had to enter into a collaborative relationship with the ATC and ensure that treatment plans made for the patient in the ATC continued when the patient returned to the referring methadone program. Conversely, the methadone program had to be assured that the patient would be maintained on methadone without experiencing bias from the ATC staff, and that the patient would not be arbitrarily detoxified from methadone in the inpatient ATC program. Once the patient returned to the methadone program after completing the ATC program, the staff of the methadone clinic had to monitor alcohol and other chemical drug abuse issues and confront noncompliance by the patient with program rules and regulations. Structural and programmatic changes required by the increased collaboration between the methadone program and the ATC include regular medical and clinical consultations, multi-agency case conferences about the patients, and development of compatible treatment policies.

The methadone patients who are referred for addiction treatment, their families and the staffs of the referring methadone programs must be knowledgeable about the rules and regulations of the ATCs and must be assured that the patients are entering a safe environment. This environment must be one in which all patient rights are protected, confidentiality is respected, and chemical abuse issues will be addressed in a therapeutic, open and honest fashion.

Program administrators in the ATCs must be alert to an unintentional establishment of a class system within the patient population by the development of separate tracks for methadone-maintained patients. To offset this possibility, the administrators developed clinical programs that encouraged group cohesion among all patients by emphasizing their strengths, weaknesses, and experiences, and the stigma and discrimination they all may encounter.

The methadone patient's motivation for treatment can be measured, like all other chemically dependent patients' motivations, by a willingness to consider behavioral changes and by an agreement to participate fully in the inpatient addiction-treatment program. As with other admissions to the ATC, the first several days to a week are critical to developing positive expectations from treatment, stabilizing the level of motivation, and establishing an environment of acceptance, professional competence and safety.

To more fully integrate methadone patients into the ATC, it is necessary to have the organization deal systemically with chemical dependence treatment, thus treating methadone as a medication. We also suggest the following organizational strategies:

- Utilizing a team approach in the treatment of the patient. This has resulted in the highest levels of retention and completion of treatment as well as the highest degree of patient satisfaction. The treatment team should consist of a physician, nurse, addiction counselor, activity therapist, and case manager from the methadone treatment program.
- Group supervision, case conferencing and educational opportunities for the staff. These are designed to provide intense peer supervision and specific training for program interventions.
- In-service lectures and training by staffs of the ATCs and the MMTs to develop an integrated approach to the treatment of methadone patients with alcohol problems.
- Visits to MMT programs by staff of ATCs and visits to the inpatient programs of the ATCs by staff of the MMT programs. The purpose of these visits is to ensure that all personnel involved in the treatment of

methadone patients with alcohol problems are knowledgeable about the treatment environments, regulations and policies of all institutions that are involved in the planning and implementation of treatment.
- Team meetings and collaborative case conferences that include staff of both the ATC and the MMT program. Also, aftercare planning must be a collaborative effort because of the discrimination that methadone patients face, which results in a lack of access to safe and drug-free housing, employment, and other needed services.

For the state-operated ATCs, methadone became accessible through the on-site pharmacies operated by the State Office of Mental Health (in the same way that any prescription medication would be accessed for the ATC patients). The Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA), granted permission to these on-site pharmacies to provide methadone to patients under existing FDA and DEA regulations. Prior to the implementation of FDA and DEA approval, access to the medication required having the patients' referring methadone treatment program or the staff of the ATC physically transport the medication from the methadone program to the ATC on a daily or weekly basis.

Staff Attitudes, Values, and Beliefs

A number of chemically dependent patients enter inpatient units of ATCs while also taking medications prescribed for a variety of medical problems. These medications do not interfere with the patient's interactions with staff and other patients. "Looking high" or complaining of fatigue is sometimes seen as an adverse reaction to many medications. Altered moods and affects such as tranquilization or fatigue may be observed with dually diagnosed patients who take both antidepressants and antipsychotics. Yet, the dually diagnosed patient on antidepressants or tranquilizers is accepted by the treatment staff of the addiction treatment centers without the bias that is directed toward the methadone patient.

As with any change, staff attitudes and their philosophical and behavioral expectations come to the forefront quickly. Gordis (11) reports that in alcohol treatment programs, staff may not consider MMT to be an acceptable treatment for heroin addicts and, therefore, deny methadone patients with alcohol problems admission into treatment. Furthermore, staff who have personal histories of chemical dependence and are in recovery themselves may favor the total abstinence model that precludes the prescription of medications such as methadone. Criticism, discrimination, and shame are not part of the 12-step philosophy, and it must be made clear to staff and patients that this attitude has no place in the inpatient program. With the intensive training that has been described, methadone patients now have access to treatment without fear of ostracism or bias in an inpatient addiction-treatment center program, if that level of care is needed.

Family involvement, education and communication are important for all patients, and especially so for methadone patients. Their families and significant others must understand not only the addiction, but also the use of methadone as a medication for the treatment of the addiction (14).

Administrative, clinical and medical staff must be informed that methadone-maintained patients have lowered thresholds of pain tolerance, and that certain pain relievers with narcotic antagonist properties do not work for them (15). Training clinical and medical staff in various alternatives for pain management is critical for patient comfort and retention. The need for immediate pain relief provides a considerable challenge for the medical staff. The patient can present with symptoms that far exceed the usual level of pain seen in most other patients. The need for immediate relief, and the stress related to this need, must be addressed in an educational, sensitive climate. When the patient's anxieties and fears are addressed, less medication can frequently be given. There is a great need for both patients and staff to learn and practice various options for pain management, coping with frustration, and relaxation techniques.

The physician and nursing staff must continually reassess the appropriate dosage of methadone to ensure the best chance of clinical success. Too often, patients admitted to the inpatient program are undermedicated prior to admission because they were abusing alcohol and other drugs and were not compliant with the treatment regimen. While methadone blood levels can be very helpful in this assessment, they are not needed for every patient. The levels are most helpful with unexplained requests for higher or lower doses by the patient, or to rule out drug interactions. The methadone maintenance program must be kept abreast of new patient information and be actively involved in the decision process when a dosage change is considered.

Conclusions

Methadone maintenance is a medically sound treatment intervention that has demonstrated efficacy in controlling drug craving: it has saved hundreds of thousands of lives (16). In 1996, OASAS made a very deliberate decision to change the policies of the ATCs to admit for treatment methadone patients with alcohol problems. Among methadone patients, alcohol is a major reason for discharge from treatment, because of behavior problems. It is also a major cause of liver disease and death. Furthermore, programs that treated alcoholism had previously refused to admit methadone patients, since methadone had not been fully accepted as a treatment for addiction. OASAS's decision resulted in the development of an educational program for the treatment staff of the ATCs; this program teaches about the efficacy of methadone in the treatment of addiction, changes in clinical programming, and collaborative relationships between MMT programs and the ATCs.

A pilot program implemented in 1997 resulted in the admission of 220 methadone patients into ATCs. About 80% of the methadone patients complied with the ATC program and completed treatment. As a result of this favorable outcome and the education provided to staff, methadone patients are now being treated for alcoholism in the ATCs, and methadone treatment is provided on the premises.

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An Alternative Program for Methadone Maintenance Dropouts:

Description and Preliminary Data

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Abstract

Time in drug treatment has been shown to be one of the best predictors of post-treatment success. Since as many as half of the enrollees leave methadone treatment during the first year, the project described in this article was designed to test the effectiveness of an alternative program for individuals who have recently dropped out of methadone maintenance treatment. The goals of this "Alternative Program" are to help participants re-connect with formal drug treatment and other community or medical programs, reduce their HIV risk behavior, decrease or eliminate drug use, join self-help groups, and obtain entitlements. Program components include: contacts by local outreach workers, cognitive-behavioral relapse-prevention group counseling, and individual counseling for needs assessment and referral. This paper describes the basis for development of the intervention, summarizes the methodology being used, and provides preliminary data on participation in the Alternative Program.

Key Words: Substance-related disorders, methadone, substance-abuse treatment centers, patient dropouts, methadone maintenance.

Introduction

WHILE TIME IN DRUG TREATMENT has been shown to be one of the best predictors of post-treatment success (1), as many as half of the enrollees leave methadone treatment during the first year (2). Other forms of treatment, such as Therapeutic Communities (TCs), a type of drug-free residential treatment, have even higher dropout rates early in the treatment process (2). Individuals who have dropped out of drug treatment may still wish to change their behavior but may have decided that the drug abuse treatment they received was not helping them to do so. Or, in line with the Transtheoretical/Stages of Behavior Change Model (3), these individuals may be in early stages of change, but not yet ready to maintain new behaviors. Therefore, these individuals may be good candidates for a tailored intervention to advance them along the continuum of change.

Little is actually known about individuals who exit drug treatment prematurely. A search of the literature reveals a paucity of reports involving those who drop out, or who fail to complete drug abuse treatment. Maddux and Desmond (4) reviewed the literature and found five long-term studies of persons who had dropped out of methadone treatment and six long-term studies of those who had dropped out of outpatient drug-free treatment. In their review, they report that while methodology, definitions of abstinence, and follow-up periods differed among the studies, the percentages found to be abstinent post-treatment ranged from 9–21% for the methadone studies and 10–19% for the drug-free outpatient studies.

There are few studies which inquire into the reasons for terminating treatment. Similarly, there are few reports of programs developed to

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re-engage or re-enroll those who drop out. Zanis et al. (5) reported on the success of telephone follow-up to those who had left a methadone program. An enhanced counseling session plus one or more telephone calls to persons who had left treatment up to one year previously resulted in a significantly greater return to treatment for the group called and counseled than for a control group (63% vs. 7%, $p < 0.01$) who did not receive such a session or follow-up call. Although the sample size in this study was small ($n = 41$), the findings indicate that efforts to contact dropouts may be effective in re-engaging them in drug treatment.

Goals of the Project

This study was designed to test the effectiveness of a program (referred to as the Alternative Program) for people who have recently dropped out of methadone maintenance treatment. The primary goal of the Alternative Program is to reconnect subjects to formal drug treatment and other community or medical programs. Other goals are to reduce HIV risk behavior, reduce or eliminate drug use, and assist in obtaining entitlements. The components of the Alternative Program include: outreach by local workers, a cognitive-behavioral relapse-prevention group-counseling strategy, and individual counseling for needs assessment and referral. This paper will: (a) describe the basis for development of the program; (b) summarize the methodology being used; and (c) provide preliminary data to assess whether methadone maintenance treatment program (MMTP) dropouts can be engaged in the Alternative Program.

Development of the Intervention

Since there were no reports in the literature on programs specifically designed for drug treatment dropouts, other sources were used as the basis for the design of the Alternative Program for dropouts from methadone maintenance. Sources included studies of (a) the effectiveness of local outreach workers in engaging out-of-treatment drug users (6); (b) the utility of the Transtheoretical/Stages of Change Model (3) in explaining health behavior change and gearing messages to the individual's "stage" of behavior change; and (c) the use of cognitive-behavioral relapse-prevention strategies for developing skills which can assist in recovery.

Role of Local Outreach Workers

The incorporation of an outreach component to engage drug treatment dropouts in a change process is an important and innovative component of the Alternative Program strategy. The rationale for this is based on the success of two types of outreaches. The first is community outreach, which has been used with increasing frequency after its demonstrated success in helping out-of-treatment drug users to modify their HIV risk behaviors including drug use itself (6–12). The studies describe how persons who were engaging in high-risk HIV-related behaviors reduced the frequency of these actions when they were approached in a non-threatening manner in their own neighborhoods by former drug users and others trained in street outreach methods, including the provision of information and materials (e.g., bleach kits and condoms) for risk reduction and referrals for needed community services. Among the behavioral changes made by addicts were: decreased sharing of injecting equipment, increased use of bleach to clean syringes, reduced frequency of injection, reduced number of sex partners, and increased use of condoms.

A second type of outreach has been utilized with success, in developing countries as well as in urban and rural areas of the U.S., to provide preventive health services. In this model, the outreach worker is usually responsible for contacting or visiting an assigned group of individuals. This method forms the basis for the training and activities of the barefoot doctors in China, TB workers and sexually-transmitted disease (STD) case workers in U.S. cities, and workers who make home visits to new mothers of high-risk infants. In these instances, the outreach worker, who is similar to the people being served, is responsible for his/her group members or caseload. The outreach worker helps the individual members of the group take specific preventive health actions. While this outreach model has not been fully developed in a theoretical framework in the U.S., elements of this role are found in the description of family health workers, neighborhood residents who were attached to health teams at community health centers in the 1960s and 1970s (13, 14). The family health worker model was developed for and used successfully in poor urban neighborhoods.

In the Alternative Program, the role of the outreach worker incorporates elements of both the street outreach worker role and the family health worker role. Several of the characteristics of outreach make it an ideal method for reaching persons who are suspicious of or uncomfortable in an established treatment system. These include:

- emphasis on non-judgmental approach
- operation outside the "system"
- location in the person's own neighborhood
- use of local individuals, including ex-addicts and others familiar with the community
- use of persuasion instead of penalties
- provision of a link to tangible services
- participation in guiding the pace of the intervention

The use of outreach methods has proven to be an acceptable format for receiving both new information and assistance in implementing behavior changes, even in communities with problems such as low literacy and extreme distrust of formal agencies.

Theoretical Framework

Stages of Change Model

Several theoretical and practical models were incorporated into the Alternative Program. The Transtheoretical Model/Stages of Change (3), which posits that a person goes through precontemplation, contemplation, preparation, action and maintenance stages when making a health behavior change, holds great promise for assisting in a change process for drug abuse treatment dropouts. The model has been applied successfully to smoking cessation, to HIV risk behaviors, and recently to treatment of cocaine abusers (15) and methadone maintenance patients (16). The first step in using this model is recognition by staff that the persons they wish to engage are likely to be at different stages on a continuum of change. "Readiness for treatment" has proven to be a good predictor of success in residential drug treatment (17) and may prove to be a good predictor of future action for other groups of drug users (18).

In the Alternative Program, the clients' stage of change guides the outreach workers and the counselor in their choice of messages. For example, in approaching pre-contemplative clients, the worker bears in mind that clients are not ready to "solve their drug problem," but may welcome "harm reduction" messages about going to a needle exchange, or bleaching syringes for the purpose of reducing or eliminating risks associated with sharing used needles. Once they have reached the contemplation stage, they may be willing to begin talking to a counselor about other kinds of change.

Relapse Prevention Model

One model borrowed from the treatment system is that of relapse prevention. Relapse prevention (19) is a widely used cognitive-behavioral skills training approach to achieving and maintaining abstinence from drugs and alcohol. In general, it consists of the following elements: (a) providing information about the biological, psychological, and social effects of addiction and recovery; (b) identifying high-risk situations and early signs of relapse; (c) developing various skills (including coping skills for achieving abstinence, behavioral skills for substituting drug-free behavior for drug use, cognitive skills such as thought stopping and cognitive restructuring for overcoming drug cravings, and affective skills for labeling and expressing emotions); (d) increasing perceived self-efficacy, to achieve and maintain abstinence; and (e) developing new drug-free lifestyle behaviors such as self-care behaviors, hobbies, and involvement in self-help activities. The Matrix Model developed by Rawson et al. (20) is in the form of a manual and contains specific topics and exercises for use in group and individual formats.

The Enhanced Reinforcement Model (21, 22) was used as a starting point for developing the group counseling component in the Alternative Program. The Enhanced Reinforcement Model is based on the Matrix Model, which was originally designed for use with middle-class cocaine abusers. The Enhanced Reinforcement Model has been implemented in a methadone program with clients similar to those in the study target population: poor inner-city residents who practice poly-drug abuse and are subject to a host of economic and educational problems. A key element in this model is providing small but meaningful interpersonal rewards for small behavior changes in the desired direction. For example, a person who completes one week in a program, may be rewarded by having his/her name and picture placed on the roster of "week-one graduates," or a person will receive praise from the counselor and group members when he/she postpones drinking alcohol until after the group session is over.

A premise of the Enhanced Reinforcement Model is that clients often have psychological vulnerabilities which make it difficult for them to manage their emotions and, therefore, to become engaged in counseling. These clients may react to minor slights or insults with inappropriate rage. After an intense burst of emotion, this type of client may avoid the counselor for several weeks or drop out altogether. According to Foote et al. (21), such reactions occur, in part, because of problems with the management of strong emotions, but also because the client may lack a basis for evaluating normal social relationships. In the present project, it was expected that successful engagement with an outreach worker would help prepare the client for therapeutic processes such as support groups and individual counseling. In these settings, clients receive further assistance in developing mechanisms for interpreting social cues and coping with their emotions.

Method

The dropout sample was recruited from two sources. The first of these is the Beth Israel Medical Center (BI) Methadone Maintenance Treatment Program (MMTP) Intake Center. Newly enrolled adult patients (age 18 and over) who are assigned to its Harlem clinics are interviewed by Alternative Program research staff, and consent is obtained to follow them if they leave treatment within one year of admission. Detailed locator information is also obtained, so that patients can be re-contacted. Project staff receive the identification numbers of dropouts from the BI Management Information Systems department on a regular basis. Letters are sent and, if necessary, telephone calls are made, to invite the dropouts for an interview at the project field site in East Harlem.

Despite these efforts, BI intake clients were difficult to re-contact, interview and recruit for the Alternative Program after they left treatment. In part, the difficulties encountered were due to clinic assignment procedures within the BI treatment system. During the recruitment period at BI, from July 1997 through June 1998, most of BI's open treatment slots were at its Harlem clinics, to which patients from diverse geographic areas were assigned. When re-interviewed at the field site, many of those who had dropped out of treatment stated that the clinic was too far from home. They also chose not to participate in the Alternative Program for the same reason.

Based on pilot work during the first year of the project, we decided to conduct street recruitment in East Harlem, to find individuals who had left treatment one year ago or less. In order to assure validation of dropout status, we asked all eight MMTPs in the immediate vicinity of the field site to provide confirmation of the discharge status of their former patients. Signed consent is obtained in the street from potential subjects by the project's outreach workers. The consents for confirmation are then faxed to the treatment programs, which generally respond within 24 hours. Recruits are asked to return the following day for a research interview. While not all recruits are confirmed, those who return for an interview are most likely to be those who have actually left an MMTP within the past 12 months. The validation process apparently discourages those who are not eligible, from returning for an interview. Using this strategy, we have been able to recruit dropouts who reside in or frequent East Harlem and who are, therefore, more likely to take part in the Alternative Program than those who were recruited at MMTP enrollment at BI. Some dropouts have already re-entered treatment by the time they are recruited for the study. These individuals are in the early phase of treatment, since by definition, they had been in treatment for less than 12 months. As such, we decided to include them in the study, and outcomes assessed for this group will include retention in drug treatment.

Eligible subjects who agree to participate sign an informed consent and are given a standardized research interview which collects information on demographics, drug use history, drug treatment history, HIV risk behaviors, attitudes toward drug treatment, and reasons for leaving treatment. All subjects are then offered an HIV test with pre- and post-test counseling. Subjects are randomly assigned to intervention or comparison groups. Those assigned to the intervention group are introduced to the program counselor and invited to a group orientation session. Those assigned to the comparison group are told that they will be invited back for a six-month follow-up interview. All subjects are subsequently contacted for six- and twelve-month follow-up interviews.

Program Description

Group Counseling

Group sessions are held four days per week. New entrants to the Alternative Program must attend an orientation session before beginning their first regular group. Subjects may attend groups for up to three months. There is a five-dollar incentive for group attendance and a bonus of three dollars at the end of the week for those who attended all four sessions. Groups are held mid-morning and mid-afternoon. Following the Matrix and Enhanced Reinforcement Models, each group session is a self-contained written module, although some modules are related by content or theme. A total of 51 sessions from these models was modified to meet the needs and characteristics of the Alternative Program participants. These characteristics include: out-of-treatment status, low literacy, continued polysubstance abuse, and lack of immediate interest in or motivation for returning to treatment. Changes were made in terminology, and language was modified to meet the needs of individuals with low literacy levels.

Individual Counseling Sessions

Each subject who is assigned to the intervention group is offered two individual sessions with the counselor during the three months of the intervention. Other sessions are offered as crisis intervention or for referrals, on an as-needed basis. The two individual sessions have been designed in the style of the group sessions — as structured exercises. The first session includes a needs assessment with regard to several types of concrete services (food, housing, medical care, etc.); determining the subject's perception of his/her drug problems; and estimating the subject's readiness for return to treatment. The second session is aimed at persuading the subject to accept a referral to drug treatment if he/she has not re-entered treatment by this time. If the subject is in treatment, the aim of the session is to encourage the individual to remain in treatment and to make the best use of the services which are available through the treatment program. The second session also helps subjects make the transition to other types of groups, such as Narcotics Anonymous, support groups, or psychological counseling groups.

Outreach Strategies

To meet the objectives of this program, the outreach workers have had to incorporate several new strategies in addition to the traditional ones of harm reduction, persuasion, appeals to improve the health of the individual, personal examples of getting off drugs, recommendations to use needle exchanges, and street referrals to concrete services. In part, this is because of the dual nature of the outreach workers' responsibilities on this project. First, the outreach workers must act as recruiters of treatment dropouts both from the BI MMTP intake sample and from the streets. Second, their deliberate contacts with the subjects are a key part of the intervention itself.

In recruiting BI MMTP dropouts, the outreach workers act as "detectives," in that they must look for persons they have not previously met. In the street recruitment strategy, the first encounter with potential subjects is on the street, but an invitation to participate must await confirmation of their program discharge status. Since this information is not immediately available, outreach workers are deprived of one of the usual persuasive recruitment strategies, namely, offering an immediate interview followed by an immediate monetary reward. However, the strategy of recruiting a person, obtaining an informed consent for validation of discharge status, and later that day scheduling an interview for the following day has proven to be successful.

As interventionists, the outreach workers have expanded their traditional street outreach role by adding aspects of what has been called the family health worker role. Once a subject has been assigned to the intervention, he/she is contacted at least weekly by the outreach worker for one month. At first, the contacts are for the purpose of getting the subject to come to an orientation session or, if the subject prefers, a one-to-one session with the counselor. Other purposes include delivering harm-reduction messages and materials (condoms and bleach kits), offering referrals which are arranged from the field site, and encouraging subjects to attend the group counseling sessions.

Staff Coordination of Services

On a weekly basis, the counselor, HIV counselor and outreach workers meet to discuss whether any subjects in the intervention group have expressed needs for services and whether staff members have noticed any significant changes in a subject's behavior or stage of change. If a need for services has been noted, the staff group decides who will make the referral and whether it is necessary or appropriate for someone to accompany the subject to the agency. If it is deemed appropriate, one of the two outreach workers will accompany the client. Usually the worker chosen is the one with whom the subject has established the greater rapport.

Toward the end of the third month of the intervention, a special effort is made to persuade those who have not already resumed treatment to accept a referral to a treatment program. Those who have re-entered treatment are encouraged to make full use of the services provided by the program. Such persuasion and encouragement is a joint effort of the counselor and the outreach workers.

Results

Description of Dropout Sample

Thus far, 426 individuals have been recruited into the dropout sample, of whom 49 (12%) are BI dropouts and 377 (88%) are street-recruited dropouts. Close to half the sample (44%) had returned to treatment by the time of the initial interview. Demographic characteristics of the sample are presented in Table 1.

Program Participation

A total of 178 subjects were randomly assigned to the Alternative Program intervention group (see Table 2). Preliminary findings of the study indicate that the majority of MMTP dropouts could be engaged in some aspect of the intervention program. Although only 30% of the subjects engaged in all three components of the intervention (outreach, group counseling and individual counseling), almost all subjects (92%) participated in at least one component. The characteristics of those who choose to participate in the different components of the Alternative Program intervention will be analyzed to determine the impact of the intervention and its separate components on involvement in drug treatment and other programs and on drug-use behavior.

TABLE 1
Description of Dropout Sample

	Number	Percent
Recruitment Source	(n = 426)	%
Program dropouts	49	12
Street recruits	377	88
Treatment Status at Recruitment		
Out-of-treatment	237	56
Returned to treatment	189	44
Gender		
Male	292	69
Female	134	31
Ethnicity		
Hispanic	239	56
African–American	106	25
White	77	18
Other	4	1
Age (mean age = 39.6)		
20–30	60	14
31–40	178	42
41–50	160	37
50+	28	7

TABLE 2
Participation in Intervention

	Number	Percent
Assigned to intervention	178	
Had at least one outreach contact (subsequent to intervention assignment)	138	78%
Had more than one outreach contact	92	52%
Attended at least one group	116	65%
Attended more than one group	98	55%
Had both group and outreach contacts	90	51%
Had at least one individual session	64	36%
Had more than one individual session	36	20%
Had at least one intervention component	164	92%
Had all three intervention components	53	30%

Findings on the Utility of the Transtheoretical/ Stages of Change Model in the Intervention

The Transtheoretical/Stages of Change Model has proven to be a useful guide in implementing the Alternative Program intervention. The counselor uses the Stages of Change Model informally to give feedback and encouragement to subjects in group and individual settings. For example, rather than press those who are in denial about a drug or alcohol problem to re-enter treatment, the worker begins by providing support in an effort to reduce substance use and other problems.

Once a subject has identified a problem, the outreach worker provides concrete assistance in solving it. For example, he/she may offer to escort pre-contemplators to medical or dental treatment, or to a Medicaid or housing office. Even those who decline such assistance express appreciation for the outreach worker's interest and support.

In group and individual sessions, the counselor presents re-enrollment in drug treatment as a desirable goal. Re-enrollment options are explored in more detail with those who express readiness to move to the action stage. Readiness is demonstrated through such statements as "I am considering going back to the methadone program" or "I really do need drug treatment." The counselor then inquires about the subject's preference for a specific program and offers to assist with enrollment.

Findings on the Intervention Components

Responses to the outreach and group counseling portions of the Alternative Program by clients who have taken part in them have been enthusiastic. Clients express a sense of loss when they realize that their three months in the program are coming to an end. Those who participate in the groups generally experience change, as reported by the group counselor. Initially, clients often hesitate to reveal their thoughts, feelings and experiences. As they become more comfortable, they begin to share experiences and emotions with others.

Since the group sessions are directed toward recognizing problems with substance use and overcoming these problems, discussion is focused on these areas. Some who enter the Alternative Program have already re-enrolled in treatment. However, they may still be using heroin and other substances. Those who are out of treatment are even more likely to be using drugs and/or alcohol. For example, 81% of those out of treatment reported using heroin, compared with 59% of those in treatment ($p < 0.001$). Few participants are solidly in the action stage of working to solve a drug problem they have acknowledged to themselves. Those in treatment are more likely to be in the preparation stage, with some acceptance of the rules of their treatment programs, but without a firm commitment to abstain from drugs. Those who are out of treatment are more likely to be pre-contemplators denying that they have a problem at all. Some out-of-treatment clients, however, are contemplators who are considering re-enrolling in treatment or using some other method to reduce or stop their use of drugs.

This client mix presents a unique challenge to the counselor. Most individuals entering drug treatment are generally prepared to proceed with treatment. Those recruited for alternative program, by contrast, are predominantly pre-contemplators. In general, those have progressed through only one stage of change during the three months of the program and are unlikely to enter treatment. Therefore, one of the objectives of the Alternative Program is to refer participants who have been socialized into the group process to various programs in the community such as Narcotics Anonymous, Alcoholics Anonymous and/or general health or mental health agencies.

Discussion

It is challenging for the outreach workers to maintain contact with clients who are often in crisis, who may be reluctant to accept referrals to services, and who are sometimes resistant to behavior change. It is especially difficult to assist clients who refuse to come to groups, are heavy users of drugs, and/or are involved in drug dealing. The most productive strategy for such individuals is to offer them harm-reduction messages and resources (e.g., for those who are drug injectors, providing bleach kits, instruction on safer injection practices, and information on needle exchanges). This "low threshold" intervention tends to promote trust and acceptance of outreach workers by the clients. For clients who are not so heavily involved with drugs but who seldom attend the groups, the outreach worker's task is to keep the individuals engaged, assist them with helpful information (for example, about food pantries, obtaining Medicaid, solving family problems, etc.) and let them know that someone is concerned about their welfare.

It should be noted that not all individuals who are selected are suitable group members. On a few occasions, individuals have had to be suspended or even terminated from the groups for misconduct, such as threatening another group member. Some individuals who have been discharged from treatment may have exhibited these problematic behaviors previously, and this may have been part of the reason for program discharge.

Conclusions

Individuals who drop out of methadone treatment can be contacted and engaged by skilled outreach workers. Effective outreach techniques include acceptance, harm-reduction messages, offers of incentives for project participation, and encouragement to use community services. More than half of these individuals will participate in a group counseling program based on a Relapse

Prevention Model if it is tailored to their needs, interests, and abilities. They will respond to a skilled and caring counselor who is trained in relapse prevention methodology and who accepts their out-of-treatment status and current drug use level. Many MMTP dropouts are still interested in change and are clearly willing to take the first steps toward recovery from drug use.

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A Mandatory Short-Term Methadone-to-Abstinence Program in New York City

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Abstract

In July 1998, Mayor Rudolph Giuliani of New York City introduced a program requiring the 2100 patients in methadone maintenance programs in selected clinics to terminate their use of methadone within 90 days. Previous short-term methadone-to-abstinence programs in California had generally been unsuccessful. Seven months of debate and controversy ensued. And several new ideas received widespread attention because of the public spotlight on this issue. In January 1999, the Mayor announced that his program had been inadequately conceptualized, was not realistic, and was being withdrawn. The wide attention given the Mayor's new program and its criticism by various authorities had led to a thoughtful examination of the whole methadone maintenance situation, with a reasonable likelihood that the situation would improve.

Key Words: Methadone, methadone maintenance.

A PROGRAM to require accelerated abstinence for methadone maintenance treatment program (MMTP) participants in some New York City clinics in 1998 led to controversy and closer scrutiny of the whole methadone treatment issue. A number of unanticipated policy changes resulted. This article examines previous short-term methadone-to-abstinence (MTA) efforts, the New York City abstinence program, and its consequences for national methadone policy.

Methadone maintenance treatment (MMT) was developed at The Rockefeller University in the 1960s, by Vincent Dole and Marie Nyswander, to deal with heroin addiction (1). They saw methadone as a medication to be used as part of a larger program that included resocialization and vocational preparation. After its approval by federal agencies and its rapid national implementation by President Nixon's Special Action Office for Drug Abuse Prevention in the 1970s, the pharmacotherapeutic dimension became paramount and the psychosocial context less salient. When it became necessary to cut methadone maintenance budgets over the years, the counseling, job readiness, vocational dimensions and other contexts of treatment were often the first to go, in New York City and elsewhere.

Since MMT was introduced as part of a treatment for long-term metabolic dysfunction, its use was implicitly long-term. In order to satisfy government regulations, it was initially necessary for treatment programs to periodically recertify the patient's need for the medication; now, however, the recertification is no longer necessary. Patients' needs for methadone, up until recently, were assumed to be open-ended.

Studies of Methadone-to-Abstinence Programs

There are no rigorous systematic studies of MTA programs. However, some information has been reported from California, where a number of MMT programs were closed, and

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follow-up data were collected on the patients whose methadone use was terminated involuntarily.

The first experience involving the termination of methadone maintenance services probably occurred in Bakersfield, California in 1976 (2). The only MMTP clinic in the city was closed and 88 of the 99 patients were unable to join another clinic, because of the remoteness of the community. These 88 patients, whose median detoxification period was 13 weeks, were compared with 89 patients then enrolled in the MMT program in Tulare, a similar rural agricultural community 70 miles to the north. Interviews were conducted with both groups two years after the Bakersfield clinic had closed. Sixty-five percent (65%) of both groups were white; 32% of the Bakersfield patients and 35% of the Tulare patients were Chicano. The mean age of both groups was around 31 at the time of the interviews.

By that time, there were clear and statistically significant differences in what had happened to the two groups. Seventy-three percent (73%) of the Bakersfield patients had been arrested, vs. 43% of those from Tulare. Comparable figures for incarceration were 65% vs. 32%. In terms of the daily use of illegal narcotics, the figures were 55% vs. 32%. For abuse of alcohol, the figures were 64% vs. 43%. Two Bakersfield patients had died of overdoses. The authors note that the Bakersfield data would have been more negative but for the high price and poor quality of the heroin available and an especially vigorous law enforcement effort during the two-year period.

Some 27% of the Bakersfield respondents were pleased that they had been able to discontinue both methadone and heroin. However, a number of patients who had been leading stable lives on MMT were thrust back into chaotic lives as street addicts, and there was a substantial net benefit from the provision of methadone maintenance in Tulare.

A similar situation occurred in Alameda County in California in 1984 (3). The county decided to stop funding MMT for persons who had occupied publicly funded slots for two years or more, had the option of being detoxified, or were paying \$160–\$200 per month at a private program. Almost all the patients had a previous history of extensive criminal involvement, and 81% had served jail and/or prison time. About half of the county's MMTP patients were interviewed at six-month intervals over a four-year period. The 143 subjects were placed by the researchers into a typology of three general types of patients:

> 1. Model patients (6%) are conventional working-class and middle-class men and women, with some education and work experience. Few have criminal backgrounds. Methadone removes the issue of drugs from their lives, and they remain in treatment a relatively short time.
>
> 2. Marginal patients (25%) are often members of the "underclass," with little education or work experience. They may arrive intoxicated at the clinic, and their spouses or companions are likely to be substance abusers. They are sometimes homeless and always live a marginal life.
>
> 3. Stabilized patients (69%) fall between model and marginal and are likely to have had a long career of using heroin and other drugs. Seeing no other alternative to remaining in the program, they gradually reduced their use of street drugs and their involvement in criminal activities.

The model patients fared best with the two-year rule; most chose to detoxify successfully. Since the marginal patients were least committed to methadone for rehabilitation, they were least affected by the new rule and most opted to detoxify and fully re-enter the heroin world.

Members of the stabilized group were hardest hit, because their income seldom permitted them to pay for treatment. Premature detoxification devastated many and convinced them that a narcotic-free life was impossible. For most of these persons, getting a job, keeping a family together, and rebuilding a life had only been possible because they were on methadone. It can be concluded that the new policy was roughest on the patients for whom methadone did the most good.

It would appear that the Alameda County policy had at least four unanticipated consequences: (1) mistrust that resulted from patients' perception of unfairness in discretionary applications of the policy; (2) damage to the clinician-patient relationship; (3) patient adjustments that were often more expensive than the MMT would have been; and (4) increases in AIDS rates as patients returned to needle use.

The research organization that conducted the Alameda investigation also compared 10 heroin users who detoxified voluntarily with 30 who detoxified involuntarily from their MMTP when funding in the San Francisco Bay area was terminated (4). This three-year study was part of a larger study of injection drug users. Four follow-up interviews were conducted with each subject and revealed that these individuals had great difficulty in paying the $160 – 200 per month for treatment, and many experienced severe destabilization in all aspects of their lives, including a return to illegal activities and partial or total abandonment of work or job training, which depended on the wellness achieved by daily methadone ingestion.

None of those who participated in the voluntary detoxification program engaged in illicit activities after they left the program. All the voluntary detoxifiers felt ready to enter an opioid-free lifestyle after the voluntary (and slow) detoxification process. The researchers, after comparing the voluntary and involuntary groups, concluded that forced premature detoxification should not be advocated. The destabilizing effect of such a policy placed heroin users at greater risk for returning to daily drug use, illicit activities, HIV, arrest and incarceration. The researchers saw the defunding as a form of harm maximization and interpreted availability of MMTP as a form of harm reduction.

Twenty-seven women who had experienced defunding from subsidized MMT slots were interviewed over a three-year period in another San Francisco Bay area study (5). Severe demoralization and destabilization of their lives were the most salient results of program loss for the women, although 7% detoxified and remained opiate-free. Most of these women found it was impossible to remain heroin-free, because they could not afford the cost of private payment. Women who held conventional jobs reported that they risked dismissal if they either revealed their MMT status to employers or were absent from work too often because of withdrawal problems.

More than a quarter of the women used Aid to Families of Dependent Children (AFDC) money, intended for their family's basic survival needs, to pay for MMT after being defunded, which resulted in less money for food, clothing, and shelter. Thirteen women returned to stealing, prostitution, and other illegal activities to pay clinic bills; ten were arrested.

While they were in the funded program, most of these women had been focusing on positive and productive goals for themselves and their families: education, work, training, a healthier lifestyle. Defunding led to participation in illicit activities, financial strains, return to heroin use, health problems, potential loss of custody of children, and other serious hazards.

The New York City Methadone-to-Abstinence Program

Despite the fact that the literature on enforced short-term methadone-to-abstinence programs is so cautionary, in July 1998, Mayor Rudolph Giuliani of New York City announced that the 2,100 methadone patients at five city hospitals would be moved to total abstinence within 90 days of the implementation of a new policy (6). The policy was a reflection of the Mayor's belief that methadone dependence is a substitute for heroin dependence and that it would be much better for the city to encourage methadone patients to take care of their own lives without medication.

Only a relatively small proportion of the 36,000 New York City methadone patients were in the hospitals controlled by the Mayor; the rest were in slots supported by federal and state funds. However, Mayor Giuliani's comments on the evils of MMT were cited by media all over America because of his fame as a very effective crime fighter and the city's pivotal role in the heroin addiction problem.

For the next seven months, the Mayor promoted and defended his policy against objections from health agencies, state and federal officials, government organizations, and researchers. The Mayor's MMT policy reflected his larger goal of removing people from welfare and placing them in jobs; about 10% of the city's welfare recipients could not work because of a substance abuse problem. In August 1998, the city clinics announced that they would henceforth only accept patients who were willing to pursue a goal of abstinence.

Nonetheless, in January 1999 the Mayor abruptly announced that he was abandoning his plan to eliminate methadone programs in city hospitals, because the short period for detoxification had proven to be too jarring and somewhat unrealistic (7). He said that he had revised his thinking on methadone after consultations with various experts. In effect, the city's abstinence goal for methadone patients was abandoned. Only 21 of the 2,100 city patients had given up methadone and five of them had relapsed to heroin use. The three-month detoxification program had proven unfeasible for the city patients (who had typically been in MMT for an average of nine years). Seventy percent (70%) were not working, and others were mentally ill or also abused other substances.

Discussion

The New York City methadone short-term withdrawal program ended abruptly and unexpectedly. There was little or no reference, in the discussions of the program, to the several California studies summarized above, which overwhelmingly document that mandatory detoxification from MMTP over a short period of time is unproductive and destructive for the majority of people whose treatment is interrupted. Some opponents of the new program tried to prove the wisdom of long-term maintenance by citing well-known studies like that by Ball and Ross (8), who found that 82% of the patients had relapsed to intravenous drug use after having been out of MMT for ten or more months.

During the seven-month period (July 1998 to January 1999) during which the Giuliani plan was being implemented, a number of important statements and studies on methadone were published. Under ordinary circumstances, these materials would probably have received little notice from the general public. But in the heated atmosphere of the time, they tended to get much media attention and public discussion. In September 1998, General Barry McCaffrey, director of the Office of National Drug Control Policy, speaking at the New York City meeting of the American Methadone Treatment Association, expressed the desire to make MMT available nationally to all who sought it and to expand "medical maintenance," so that physicians could write prescriptions for methadone as they would for any other drug (9).

McCaffrey, a four-star general who had been a hero of the Gulf War, and a dignified conservative who had previously been associated with a more hardline approach, became a leading spokesman for methadone maintenance. Although Giuliani used emotionally toned language in denouncing him, the general was very careful and professional in his comments, praised the Mayor's record in fighting crime, and referred to the larger needs of the country and New York City in dealing with the opiate problem. The mass media implicitly contrasted the message and language of the two men, to the detriment of the Mayor.

In a journal article published in October 1998 (10), Dr. Alan I. Leshner, head of the National Institute on Drug Abuse, set forth the concept of addiction as a chronic, relapsing disease of the brain, for which the social contexts in which it both has developed and is expressed are critically important. He suggested that a reasonable standard for treatment success is managing the illness rather than curing it. In an interview, Leshner observed (11) that "probably the biggest disservice that has been done to getting effective treatment to heroin addicts is the inaccurate statement that methadone is a heroin substitute. . . . We think science should replace ideology on how we deal with treatment in this country."

In December 1998, the statement of an NIH consensus panel on the treatment of opiate addiction was published in *JAMA* (12). The report stated that opioid dependence is a medical disorder rather than a problem of motivation or willpower and most, if not all, MMT patients require continuous treatment over a period of years and perhaps for life. That is, the report stated, why the program is called methadone "maintenance" treatment.

The article by Leshner and the report of the NIH panel appeared in journals that schedule articles for publication months or years in advance, so that their appearing in the midst of the Giuliani policy debate was an extraordinary coincidence. Since the Giuliani policy had generated so much interest, the general's speech and the two scholarly journal reports were treated as major news events by the mass media and led many reporters to interview various authorities to get comments on how these materials contributed to the New York City methadone debate. Nearly all the editorials and authorities cited by the media during the half year of discussion expressed strong opposition to the Giuliani policy. The media summaries and allied comments by others clearly had some impact on the Mayor. In announcing his reversal of his policy, the Mayor said (7), "I listened to the debate . . . . I really do listen and read what people say and write." Like most of the developments in the debate over the methadone policy, the news of the Mayor's recantation was carried on the front page of the *New York Times*, the city's most influential newspaper.

The avalanche of publicity helped bring about a more realistic awareness of how methadone maintenance might be improved, and led to actual program improvements. The half year of rigorous debate over methadone maintenance policy, in which the Mayor was presented by some media as a rigid ideologue who was taking away a major centerpiece of the life of a downtrodden group of people, probably helped to give MMT a much more sympathetic image than it had previously enjoyed. Because MMT is so heavily stigmatized, methadone patients tend to avoid publicity, and there are very few who will identify themselves as such, in contrast to celebrities who are eager to write books and give interviews about their stay at the Betty Ford Clinic, Hazelden, or other publicized residential treatment programs.

It is ironic that Mayor Giuliani was probably responsible for improving the image of, and permitting others to present the genuine merits of, methadone maintenance in a manner that had rarely been possible since the program began 35 years ago. Another unanticipated consequence is the expansion of vocational services for other methadone patients after the Mayor announced that he was providing intensive vocational rehabilitation services for the patients who would be in the short-term withdrawal programs.

The Mayor's announcement helped to call attention to the role of vocational-related training, not only in New York but also in the national approach to methadone treatment. In the first decade following the development of MMT, many patients were helped to become socially productive by programs that included job readiness, and vocational and related kinds of training. Unfortunately, the recession of the 1970s, subsequent changes in the job market, and the growing importance of information technology in the economy led to a substantial decline in the availability of jobs that did not require special training. In the last two decades, persons without such training, who represent a majority of the MMT patient population, have found it increasingly difficult to achieve successful integration into the workforce. Such considerations became significant elements in the discussions and reevaluation of methadone treatment, which followed the Giuliani debate. Subsequently, the Mayor allocated $5 million for social services at the methadone clinics. These services would be under the supervision of the Health and Hospital Corporation and include (for the first time) plans for lower patient-to-counselor ratios, and placing patients in different "treatment tracks" according to their needs.

The public reversal of a nationally important politician like Mayor Giuliani, and his willingness to admit that he had made an inappropriate judgment, had extraordinary impact in positively presenting the methadone maintenance modality. The general public and the various professional groups in America were made aware or reminded of the realities of a form of treatment that has so often been misrepresented. Another possible benefit of the debate could be a careful and well-designed prospective study of the outcomes obtained through implementation of the plans described above.

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Analysis of Behavioral Patterns in Five Cohorts of Patients Retained in Methadone Maintenance Programs

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Abstract

Background: Various techniques have been devised to evaluate the effectiveness of long-term methadone maintenance treatment. Traditional comparative analysis of behavior patterns at the time of admission and discharge would be inappropriate, because the majority of patients leave the programs prematurely and under unfavorable circumstances. One approach has been to collect available data on patients who are actively undergoing methadone treatment.

Methods: The sampling population for this study was limited to methadone maintenance patients in New York State who have remained in treatment for 1 – 6 years. Samples of active patients were drawn from five time-in-treatment cohorts (1 – 2 years, 2 – 3 years, 3 – 4 years, 4 – 5 years and 5 – 6 years). A total of 673 patients were included in the study.

Results: All five cohorts experienced significant reductions in the number of patients arrested, the number of patients incarcerated, and the number of days incarcerated per patient. Each cohort also experienced large reductions in arrests per patient and moderate increases in employment-related activities, although current rates of employment are still relatively low. A decreased number of child-protective cases were noted over time for those under treatment, along with higher rates of insurance and self-pay for treatment. The self-pay group, however, remained relatively small. No patterns were detectable in the areas of patient hospitalization or emergency room admissions, although the 5 – 6 year cohort experienced reductions on all measures.

Conclusions: Some favorable changes in the behavior of patients are associated with long-term methadone treatment.

Key Words: Methadone maintenance, evaluation.

Introduction

The New York State Office of Alcoholism and Substance Abuse Services (OASAS) is responsible for the licensing and/or funding of approximately 1300 treatment programs throughout the state. It monitors the effectiveness of these programs, utilizing a combination of ongoing evaluation systems, treatment outcome studies and analysis of data submitted by programs to the OASAS Client Data System (CDS). Through the data submitted on the admission and discharge forms of the CDS, OASAS obtains demographic and treatment progress information on all patients admitted into the system. In 1997, a report on the impact of alcohol treatment and non-pharmacological treatment for drug abuse was issued (1). It demonstrated the positive change in patient behaviors for those who remained in treatment at least six months prior to discharge (e.g., reduced arrests, reduced incarcerations, reduced emergency room [ER] admissions).

Methadone maintenance is a modality of treatment for those diagnosed with opiate dependence (primarily heroin dependence) of at least one year's duration. After the patient consumes a clinically adjusted daily dose of methadone hydrochloride, a long-lasting analgesic, a stable opiate metabolic level is produced for 24 – 36 hours. A clinically adjusted dose is neither intoxicating nor does it impair motor or mental functioning or produce uncomfortable side effects. After beginning a methadone maintenance treatment (MMT) regimen, a heroin addict soon reaches a stable, non-euphoric state. Some individuals may become more amenable to counseling and other social services that can attempt to shift lifestyles away from the previous drug-seeking

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behaviors, including criminality, toward more productive, socially acceptable behaviors, such as furthering education and obtaining employment. In New York State, there are more than 40,000 patients in licensed methadone maintenance programs, of whom nearly 90% currently have been in treatment for six months or longer.

Unlike drug-free treatment programs, methadone maintenance programs encourage most patients to remain in treatment for extended periods, due to persistent physiological changes in brain functioning resulting from chronic use of heroin (2–4). Methadone maintenance acts as a corrective procedure, since changes reappear after methadone is withdrawn. It is known that high heroin relapse rates and death rates occur among those who leave methadone maintenance programs because of noncompliance, or against clinical advice prior to completing 6 months of treatment (5–8). This study collected data by surveying those patients who had been retained in methadone treatment programs.

Methods

Utilizing the OASAS CDS, the random sampling procedure available in the SPSS (Statistical Package for the Social Sciences) software package was used to sample 144 cases from each of the following cohorts:

1. Patients in treatment one year or more but less than two years (6,502)

2. Patients in treatment two years or more but less than three years (4,997)

3. Patients in treatment three years or more but less than four years (3,981)

4. Patients in treatment four years or more but less than five years (3,901)

5. Patients in treatment five years or more but less than six years (2,508)

It should be noted that of 12,264 patients discharged from methadone treatment during 1998, 8,531 (67.6%) had been in treatment less than two years; 1130 (9.0%) had been in treatment between 2 and 3 years; 738 (5.8%) had been in treatment between 3 and 4 years; 545 (4.3 %) had been in treatment between 4 and 5 years; and, 350 (2.8%) had been in treatment between 5 and 6 years.

Based on a statistical power analysis, it was determined that surveys of approximately 130 patients in each of the five cohorts would have to be obtained in order for the data to be generalizable to all patients fitting the criteria. A survey form was developed, and program and patient identifying data were inserted onto the forms. Programs in which the selected patients were active were identified, and letters were sent to the directors asking for their participation and requesting that the program designate a staff person to serve as a study liaison to facilitate the completion and return of the surveys. The study required the participation of 107 (out of a total of 126) methadone programs in New York State. All programs agreed to participate.

Once the liaisons were identified, 720 surveys were mailed (for 144 patients in each of the five cohorts). Most programs completed all the required forms promptly. For a few programs, repeated attempts were required in order to get them to comply. Several programs were excluded from the study (34) due to closure of the program or the fact that all patients selected had previously been discharged and were no longer active. Most of these programs had only one patient selected, however, so that only 47 of the original 720 patients were excluded, resulting in an actual sample of 673 patients in 73 programs. After 4.5 months, all completed surveys had been submitted.

Survey questions focused on several key variables believed to be good indicators of patient behavior. Data were collected in the following areas:

1. **Arrests.** The average number of patients arrested in the six months prior to admission, as compared to the six months preceding the survey; the change in the numbers of patients arrested during the comparable periods was then calculated.

2. **Incarceration.** The average number of days incarcerated in the six months prior to admission, as compared to the six months preceding the survey; the change in the numbers of patients incarcerated during the comparable periods was then calculated.

3. **Hospitalization.** The average number of days hospitalized per patient in the six months prior to admission, as compared to the six months preceding the survey; the change in the numbers of patients hospitalized during the comparable periods was then calculated.

4. **Emergency room utilization.** The average number of ER episodes per patient in

the six months prior to admission, as compared to the six months preceding the survey; the change in the numbers of patients with ER episodes during the comparable periods was then calculated.

5. **Educational/vocational status.** The total number of patients with a high school diploma or G.E.D. at admission and at the time of the survey; and the total number of patients employed, in training, or in school at the same points in time. Work Experience Program (WEP) data were collected on the survey (these data were not available in the admissions data).

6. **Method of payment.** Mode of patient payment for services at the time of the survey.

7. **Child-protective cases.** Number of active child-protective cases involving patients at the time of the survey or in the prior six-month period.

8. **Current living arrangements.** Patient domicile at the time of the survey.

For patients in the one-year and two-year cohorts, current behavior, as determined by survey data, was compared to the same behaviors as assessed on the OASAS Client Admission Report. For those patients in treatment longer than three years, data on arrests, incarcerations, hospitalizations and emergency room use in the prior six months were not included in the Client Admission Report. In July 1995, the Client Admission Form, an OASAS standard form used throughout New York State, was modified to include the data on arrests, incarcerations, hospitalizations, and ER use during the prior six months. Because patients in the cohorts that were in treatment three to five years were admitted prior to July 1995, when collection of the information of interest began, it was necessary to devise an alternative method of estimating pre-admission experience for these cohorts. This was accomplished by assuming that the pre-treatment behavioral patterns for patients admitted to treatment prior to July 1995 were the same as for patients admitted subsequently. Based on this assumption, the in-treatment experience of patients in treatment three to five years was compared with the pre-admission experience of all patients admitted during the first year the pertinent data items were collected: that is, July 1995 through June 1996 (n = 4,085). This constitutes a representative admission cohort with respect to the ultimate length of time in treatment (albeit greatly censored at the time of the study). It also includes patients who would eventually have been eligible for inclusion in the longer-term cohorts with which they are being compared.

Results

In total, 673 completed surveys were received. The breakdown by cohort is presented in Table 1. The number of completed surveys ranged from a low of 129 for the one-year cohort to 144 for the two-year cohort. The number of completed surveys in each cohort was sufficient to conduct statistical analysis. The percentages of males and the different ethnic backgrounds of patients varied by cohort, although the actual percentages in the total methadone maintenance population remained very stable. The cohort variability was a function of the relatively small samples selected for analysis. It appears that the effect of excluded data from the original sample on the outcome was minimal, however, due to the relatively small number that were excluded. The age of the patients increased moderately with the length of time in treatment, from 40.4 for the 1 – 2 year cohort to 43.2 for the 5 – 6 year cohort.

TABLE 1
OASAS Evaluation Systems: Methadone Maintenance
December 1998
Patient Demographics by Cohort

Cohort	Number of Cases	% Males	% Black	% White	% Hispanic	Average Age
1 – 2 years in treatment	129	62%	30%	38%	32%	40.4
2 – 3 years in treatment	144	67%	25%	36%	38%	41.0
3 – 5 years in treatment	135	70%	29%	26%	46%	41.0
4 – 5 years in treatment	134	62%	37%	27%	36%	42.4
5 – 6 years in treatment	130	65%	29%	33%	38%	43.2

Arrests

A large majority of patients (80% and above) were not arrested in either period. In the cohorts for which we have both pre and post data, the maximum number of patients arrested is 23, or 19%.

Data suggest that admission into MMT has a favorable impact on the arrest rates for patients that remain at least one year. Although the level of change for the two-year cohort (−59%) is not significant, it is part of a pattern of decreasing arrest rates for the two-year through five-year groups. Significant changes range from −75% for the three-year cohort (from 0.17 per patient to 0.07 per patient) to −89% for the one-year cohort (from 0.47 per patient to 0.05 per patient). The above data are presented in Figs. 1 and 2.

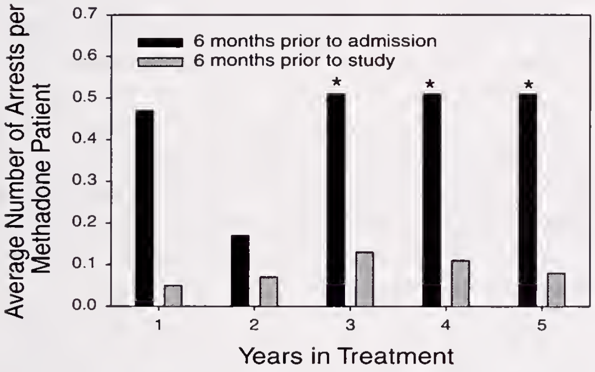

Fig. 1. Average number of arrests per methadone patient. *Combined 1 – 3 year comparison group. $p < 0.01$ for 1, 3, 4, 5 year cohorts. (New York State Office of Alcoholism and Substance Abuse Services, Bureau of Planning and Evaluation)

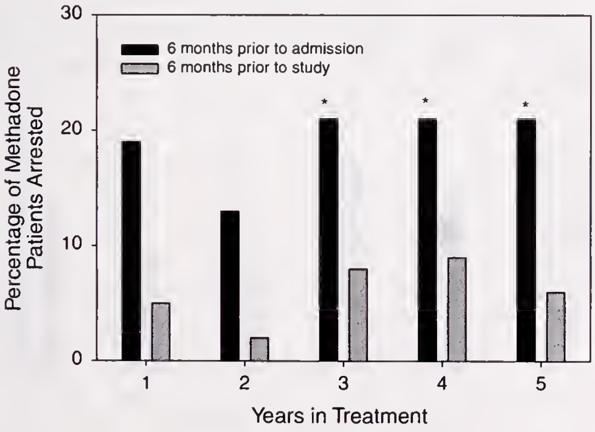

Fig. 2. Percentage of methadone patients arrested. *See Fig. 1. $p < 0.01$ for all cohorts. (New York State Office of Alcoholism and Substance Abuse Services, Bureau of Planning and Evaluation)

Incarceration

A large majority of patients (84% and above) in all cohorts did not serve any time in prison during either period. In the cohorts for which we have both pre and post data, the maximum number of patients incarcerated is 18, or 15%. Changes in days incarcerated per patient ranged from −88% for the two-year cohort (from an average of 7.6 days of incarceration to an average of 0.9 days of incarceration) to −95% for the five-year cohort (from an average of 9.5 days to an average of 0.5 days).

All five cohorts demonstrated decreased numbers of patients incarcerated in the six-month period prior to the survey. Changes ranged from -52% for the three- and four-year cohorts (both going from 16% or 21 patients incarcerated in the six months prior to admission, to 7% or 10 patients incarcerated in the six months prior to the survey) to -83% for the two-year comparison group (from 15% or 12 patients incarcerated to 4% or 5 patients incarcerated). The above data are presented in Figs. 3 and 4.

Hospitalization

Only a small percentage of patients in either period were hospitalized. For those patients for whom we have both admission and survey data, the maximum number of patients experiencing a hospitalization is 19, or 15%. Thus, a great majority of these patients were not hospitalized during either period.

There is no discernable pattern in the change of the average number of days hospitalized per patient. None of the changes are significant.

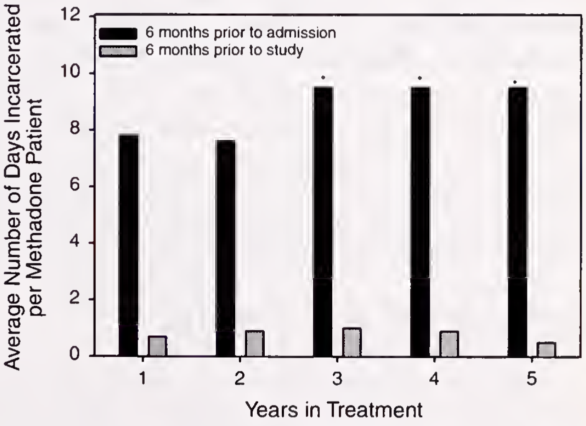

Fig. 3. Average number of days incarcerated per methadone patient. *See Fig. 2. (New York State Office of Alcoholism and Substance Abuse Services, Bureau of Planning and Evaluation)

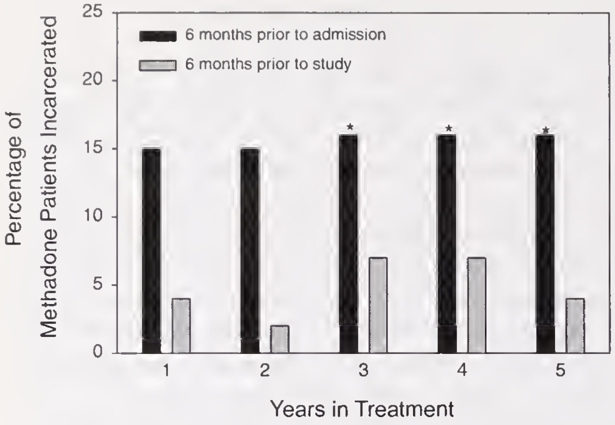

Fig. 4. Percentage of methadone patients incarcerated. *See Fig. 2. (New York State Office of Alcoholism and Substance Abuse Services, Bureau of Planning and Evaluation)

The pre/post change of patients hospitalized from the one-year cohort to the three-year cohort peaks at +83% and then drops until, for the five-year cohort, there is a 25% decrease in the percentage hospitalized (from 9% or 12 patients hospitalized during the six months prior to admission, to 7% or 9 patients hospitalized in the six months prior to the survey). However, since only the change for the three-year cohort reached significance, it is difficult to determine if this is a valid pattern.

Emergency Room Episodes

An examination of the data reveals that a large majority of patients did not use the ER. Among those patients for whom we have admission or survey data, the maximum is 16%. There is no particular pattern of changes in the average number of ER episodes from the six months prior to admission to the six months prior to the survey. In addition, none of the changes are statistically significant. The data on the number of patients using ERs displays the same lack of consistent patterns and statistical significance. However, for both measures, the five-year cohort experiences a reduction in the average number of ER episodes per patient and total number of patients using ERs. This is consistent with the findings for hospitalizations.

Educational/Vocational Status

In all cohorts other than the first, some patients appeared to "lose" educational achievement. In two cohorts (two-year and four-year), the percent losing was nearly as great as those gaining. In the five-year cohort, the number losing was more than four times that of those gaining. The "loss" of educational status can probably be attributed to inaccurate patient reporting at admission (e.g., patients saying that they completed high school when in fact they had not) or poor data recording.

The number of patients employed, in training or in school at admission and at the time of the survey were compared (see Fig. 5). All five cohorts demonstrated increases; only the increases for the three-to-five-year cohorts were significant. Admission rates ranged from 17% (four-year cohort) to 31% (two-year cohort). Survey rates ranged from 32% (one-year cohort) to 39% (two-year and five-year cohorts). Increases ranged from 6.4% for the one-year cohort to 18.3% for the four-year cohort. For the latter, the rate more than doubled (from 16.7% to 35%).

Relatively small percentages of patients in each of the five cohorts are currently in WEP, operated by county social services offices. Values ranged from 3% for the four-year cohort to 9.6% for the two-year cohort. At this time, there is no way of knowing whether these percentages represent the numbers of patients in each cohort actually screened, the number found eligible for WEP, or some other factors.

Method of Payment

The percent of patients self-paying or paying through insurance shows an increasing trend from a low of 16.3% for the one-year cohort to a high of 26.4% for the five-year cohort. Likewise, the percent of patients having governmental support pay for their

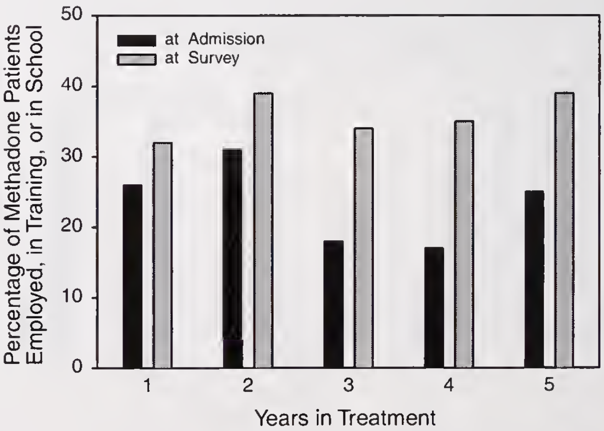

Fig. 5. Percentage of methadone patients employed, in training, or in school. $p < 0.01$ for 3, 4, 5 year cohorts. (New York State Office of Alcoholism and Substance Abuse Services, Bureau of Planning and Evaluation)

treatment displays decreasing trends from a high of 79.8% for the one-year cohort to 72.8% for the five-year cohort. Those patients with no source of payment (essentially treatment paid for by OASAS Local Services funds) display similar decreases, from a high of 3.9% for the one-year cohort to a low of 0.8% for the five-year cohort (see Table 2).

Child Protective Cases

The one-year cohort has a low level of child-protective cases (3.1%), with the rate peaking at 6.9% in the two-year cohort. Thereafter, the rate generally decreases back to the one-year cohort level.

Current Living Arrangements

All cohorts demonstrated slight, but nonsignificant increases in the percent of clients living alone at the time of the survey.

Discussion

This report describes the analysis of patient data submitted by methadone maintenance treatment programs (MMTPs) to the OASAS Client Data System. The data are based on patient self-report. Although an experimental design was not employed and a control group was not utilized, the data presented in this report convincingly demonstrate the effectiveness of methadone programs in reducing the negative consequences associated with the illegal use of opiates. The data also support the findings that long-term, uninterrupted MMT produces the best outcomes (9). Although the confirmation of long-term longitudinal outcomes of individual patients will have to await the results of the OASAS Treatment Outcome Study and its Treatment Outcomes Prospective Studies (TOPS) II Study, the positive patient status found in this study bodes well for such findings.

The findings of this study are consistent with other research that has been conducted. Research on the impact of drug and alcohol treatment on criminal activity reveals significant decreases at follow-up (10, 11). Almost all such studies demonstrate that the number of criminal activities of patients that remain in MMT is significantly lower than that for those who leave treatment (9). OASAS' expectation is that patients who remain in treatment would experience a decrease in their involvement with the criminal justice system. The examination of patient arrests was one way of measuring this involvement. Although the number of arrests can be impacted by factors other than criminal activity by the patient (e.g., variations in local police reporting regarding drug use in their community), it is one of the standard measures used in assessing the impact of drug and alcohol treatment. The findings demonstrate that patients who remain in methadone treatment for at least one year experience fewer arrests. Those who stay two years appear to experience decreases to a smaller degree. However, significant decreases continue to be demonstrated for those who have remained in treatment for between three and five years.

Along with arrest data, time spent in jail or incarceration is a commonly used measure of patient criminal justice involvement. The large reductions found in the percentages of patients incarcerated and the number of days of incarceration further demonstrate the effectiveness of long-term MMT in decreasing patient involvement with the criminal justice system.

Assessing the impact of drug and alcohol treatment on patient use of medical or

TABLE 2
OASAS Evaluation Systems: Methadone Maintenance
December 1998
Method of Payment

Cohort	n (%) of patients with self or insurance payment	n (%) of patients with government support	n (%) of patients with no source of payment
1 year	21 (16.3%)	103 (79.8%)	5 (3.9%)
2 years	37 (25.7%)	105 (72.9%)	2 (1.4%)
3 years	26 (19.3%)	102 (79.2%)	2 (1.5%)
4 years	29 (21.6%)	103 (76.9%)	2 (1.5%)
5 years	34 (26.4%)	94 (72.8%)	1 (0.8%)

psychiatric hospital (inpatient) services is a complex task. Many patients admitted into treatment for drug and alcohol abuse have been preoccupied with the acquisition and use of these substances. They are very likely to have neglected their physical health needs for extensive periods of time. Many had neither private insurance coverage nor Medicaid prior to admission to an MMTP. The primary problem that medical hospitalizations in the six months prior to treatment might reflect would be extreme situations brought on by extended neglect. This is particularly true for MMTP patients. These patients are primarily heroin injectors who present with a host of significant health problems and diseases, including sexually transmitted diseases, tuberculosis, hepatitis C and AIDS. In addition, many psychiatric symptoms are often masked by substance use or are misinterpreted as symptoms of use. As a result of both of these factors, patient utilization of hospital care may be relatively low in the six months prior to treatment. Upon treatment admission, methadone programs are required to provide patients with a physical examination. This increased attention to patient physical health may reveal serious medical problems that require hospitalization. Patient discontinuation of drug/alcohol use upon treatment admission may reveal or exacerbate serious existing mental health problems requiring psychiatric hospitalization. Thus, though seemingly counterintuitive, it is possible that patients may demonstrate increased use of hospitalization after they have been admitted to MMT. The expectation, however, is still that the longer the patient remains in treatment, the greater the long-term reduction in the use of hospitalization. The impact of MMT on hospitalizations is unclear based on the data found in this study. However, it appears that by the fifth year of treatment, there is a reduction in the percentage of patients hospitalized and the number of days spent in hospitals.

Inappropriate use of ERs is a major contributor to the spiraling costs of health care. Many persons without a family physician use the ER as a substitute for primary medical care. In addition, many persons with family physicians or access to a medical clinic may use an ER in the evenings or on weekends when the presenting medical condition is not critical. One of the goals of managed care is to reduce the inappropriate use of ERs, thereby reducing health-care costs. Although the findings regarding ER usage are consistent with those for hospitalizations, it is not clear whether this trend is real or due to chance.

Although there will always be a certain percentage of patients who, due to various psychological, physical or sociological factors, will remain “unemployable,” the majority of patients, given the appropriate level of education and training, can become gainfully employed. The long-term success of any treatment is in many ways dependent on such achievements. The “loss” of educational status apparent in a majority of cohort groups in this study can probably be attributed to inaccurate patient reporting at admission (e.g., patients saying they had completed high school when in fact they had not) or poor data recording. Given OASAS’ increased emphasis on improving the quality of data reporting over the last three years, the fact that most problems occurred with the five-year cohort and none with the one-year cohort, suggests that poor reporting may have been the dominant factor. At this time, there is no way of knowing whether the percentages reported for patients in WEP represent the numbers actually screened in each cohort, the number found eligible, or some other factors. The educational and employment data generally demonstrate improved patient status for those remaining in treatment for one to five years. However, the overall percentage of those employed is quite modest and suggests that methadone programs must place increased emphasis on these areas in order to obtain greater gains.

It is generally assumed that, as patients become rehabilitated, a change in their method of payment for treatment services will occur. The pattern expected is a decrease in payment by governmental support services — e.g., Social Security Insurance (SSI), Temporary Assistance for Needy Families (TANF), Safety Net — and an increase in self-payment and payment by insurance companies. TANF and Safety Net were created by the NY State legislature in 1997, replacing the prior welfare system. The data collected show the same modest positive trends demonstrated by the employment data. This is not surprising, since the two are closely linked. Unless patients become employed, there is no reason to expect an increase in their ability to pay for treatment themselves or through private insurance. Therefore, larger decreases in government support can only be expected if increased emphasis is placed on educational and employment-related services.

Some patients enter treatment in anticipation of, or as the result of, a child-protective case. The assumption is that the patient's use of illegal drugs is contributing to the factors leading to the need for child protection and that drug treatment may contribute to the amelioration of those factors. The results suggest that patients may be entering treatment anticipating child-protective cases that do not actually occur until their second year of treatment. Since patients remaining in treatment begin to improve their behavior and stabilize their lifestyles, one might expect a more positive resolution of their child-protective cases. Thus, the positive impact of treatment might be demonstrated by the return to the low rate of child-protective cases at one year by the four- and five-year cohorts. However, since the cohorts consist of different patients, it cannot be determined whether this pattern would be valid in a longitudinal examination of the same patients. Such a determination would require further study of this specific issue.

A patient's living arrangements can have a crucial impact on his or her ability to discontinue the use of illegal substances. However, the impact of living arrangements may be either positive or negative. If a client is living with someone who uses illegal substances or abuses alcohol and who is not in treatment, the patient's ability to successfully rehabilitate may be compromised. Conversely, if the patient is living with someone who does not use illegal drugs or abuse alcohol and who is supportive of attempted rehabilitation, the patient's chances at successful treatment are greatly enhanced. One of the frequent goals of drug or alcohol treatment is to get the patient to remove himself or herself from a destructive, drug-using living situation. Based on this study, it does not appear, however, that retention in MMT has a meaningful impact on a patient's living arrangements.

Demographic data did not reveal any unexpected trends. It is interesting to note, however, that the information obtained regarding patient age suggests that most patients who enter treatment in their late thirties remain for longer periods of time.

There were a number of inherent weaknesses in our study. First of all, desirable changes identified pertain only to experiences of patients while in treatment; post-treatment experiences are not addressed. However, since the philosophy of methadone treatment is to keep patients in treatment for long periods, possibly for life, we do not believe that this limitation constitutes a serious flaw.

There is also the issue that patients in treatment for less than a year are excluded from the study. Although this constitutes only about 22% of the in-care population, more than one-half of the patients admitted to methadone treatment are discharged prior to spending a full year in treatment, meaning that a majority of patients who receive any methadone treatment would never be eligible for inclusion in this study. Again, we do not view this as a serious weakness. In fact, it was done deliberately, because it was felt that patients in methadone treatment less than one year would not have experienced enough treatment to produce a favorable outcome on the measures used in this study.

Perhaps the greatest weakness of this study is in the limitations of the methodology. Collection of admission data beginning in July 1995 allowed, for the two shorter-term cohorts, statistical analysis to be conducted using methods that took advantage of the fact that we had data points available for the same individuals at both points in time. The absence of some admission data for the three longer-term cohorts, however, meant that for these groups we had to use aggregate admission data as a proxy for what actual admission data would have looked like for the longer-term patients actually in the study. This seems a reasonable assumption, but one that did not have to be made for the shorter-term clients, for whom we had a more complete set of admission data.

The results of this study suggest that many favorable changes in client behavior occur, based on their remaining in MMT. Further research may be needed to more fully establish these relationships over time.

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Selected In-Treatment Outcomes of Long-Term Methadone Maintenance Treatment Patients in New York State

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Abstract

The New York State Office of Alcoholism and Substance Abuse Services (OASAS) licenses the largest system of methadone maintenance clinics nationwide. In 1996, a survey was undertaken to evaluate the functioning of patients continuously active in treatment for ten or more years. Information was obtained on a 10% random sample from the OASAS client data system and the records of the clinics. Data were collected concerning methadone dose, illicit drug and problematic alcohol use, employment, criminal activity, health, living situations, and the primary type of payment for treatment. A contrast group was constructed of discharged patients who had no more than 5 years of continuous treatment. The long-term active patients in the study sample showed superior outcomes on all variables, although some of the differences were small. However, the arrest rate for the discharged contrast group was 20 times as large as the arrest rate for the active study sample. These results are consistent with nationwide evaluations of methadone maintenance treatment. Factors that negatively impacted on the adjustments of the active patients were heavy use of crack/cocaine and disabilities. The long-term active patients in this sample belong to distinct subgroups with different levels of functioning, achievement, and ongoing health and social needs that must be investigated and addressed.

Key Words: Heroin addiction, methadone maintenance, outcomes, long term treatment.

Background

IN 1996, A NEW YORK STATE LEGISLATOR introduced a bill to limit the length of methadone maintenance treatment (MMT) to 18 months. The advocacy and political activity which thwarted the bill led to an interest in whether the effectiveness of MMT shown in nationwide studies applied to New York State's own MMT system (1). Furthermore, concern with the cost-effectiveness of state-supported alcohol and other drug (AOD) treatment services, fueled by the pressures of welfare reform and managed care, also contributed to an interest in the effectiveness of MMT, since the New York State Office of Alcoholism and Substance Abuse Services licenses the largest system of methadone clinics in the United States (2).

As a result, the single state agency which funds and certifies AOD treatment in New York, the Office of Alcoholism and Substance Abuse Services (OASAS), initiated an assessment of treatment effectiveness of programs that treat substance abuse in New York State, including MMT. The study focused on an important but rarely addressed issue in MMT evaluation research, namely, the current functioning of MMT patients in treatment continuously for very long periods.

As the site of initiation of MMT and with a large AOD treatment population, New York presents a unique opportunity to explore the adjustments of very long term patients. For this study, "long-term" was defined as 10 or more years of continuous treatment with no more than one 90-day interruption. An interruption was included to accommodate clinical and reporting contingencies that would have inappropriately excluded patients actually enrolled continuously. Methadone Medical Maintenance patients, a small subgroup of well-rehabilitated patients treated in private medical practices, were excluded. Only patients treated in standard congregate care clinics were assessed. New data were collected for the 10-year patients for the six-month period before the study began in August 1996. In addition, data were collected from a contrast group drawn from the patient cohort discharged in 1996; this group had had three months to five years of continuous MMT experience, i.e., a meaningful but shorter treatment experience.

Design

Treatment durations for methadone maintenance patients are intended to be indefinite and, perhaps, lifelong for most

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patients. Despite the importance of treatment longevity in MMT, however, there have been few studies of the in-treatment outcomes of long-term MMT patients. This study was conducted to obtain data on patients in treatment continuously for at least 10 years (which could include one interruption of up to 90 days). Our objectives were to determine (a) the size of the patient population in treatment at least 10 years and (b) their drug abuse, criminal justice, medical, employment, and related outcomes as compared to those of patients discharged after a shorter treatment experience.

Method

The data collection strategy involved a one-page form for MMT program counselors to complete on those patients in their caseload who, according to OASAS' Client Data System (CDS), met the treatment tenure criterion. Treatment and outcome data requested included current methadone dose, measures reflecting illicit drug and problematic alcohol use, employment, criminal activity, health, living situation, educational status, and primary method of payment for MMT services. Where relevant, data were requested for the six-month period preceding the request.

Procedure

This study was part of a three-pronged effort funded by the federal Center for Substance Abuse Treatment (CSAT) and subcontracted to Research Triangle Institute (RTI), to assess MMT program functioning and outcomes in New York State. A letter from OASAS' commissioner went to all MMT providers in New York State (NYS). It discussed the need to develop information on MMT outcomes and their cost-effectiveness for patients in NYS, to determine whether they agreed with the results of nationwide studies (1, 3).

Provider cooperation was requested in filling out a data collection form for each active patient in their clinic(s) who met the "10-year plus" continuous treatment criterion. Shortly afterwards, all providers were sent instructions for completing data collection forms, and a copy of the printout for their 10-year patients who OASAS' Client Data System (CDS) determined to be active as of August 1996.

The patient survey form requested: MMT provider name and number, Program Reporting Unit (PRU) number (note: this number is a code number assigned to a specific treatment site), patient identification number, years in treatment (rounded to the nearest whole year: less than six months versus six months or more), patient Medicaid eligibility, employment status, years and months continuously employed full-time if patient was employed full-time, highest school grade completed, type of residence, alcohol as a current problem, current dose (in mg), the primary method of payment for MMT services, weekly contribution in whole dollars if the patient was self-paying, and, in the past 6 months: the number of urinalyses which were positive for illicit drugs, the number of emergency room admissions, the number of arrests, and the number of days hospitalized for non-detoxification services.

In addition to the patients meeting the 10-year, continuous treatment criterion, we were also interested in other patients to whom these patients might be compared. In other words, how might treatment outcomes differ for patients who stay 10 or more years and those who leave after a meaningful but shorter period of treatment? Those in the group (referred to subsequently as the "contrast group") who had the most complete outcome data were patients who had three months to five years of continuous treatment and who had been discharged during the first half of 1996. (The wide span of treatment intervals included in the contrast group is based on Treatment Outcome Prospective Study (TOPS) findings (1) that the bulk of clinical gains after admission to MMT occur after about three months, with real but much smaller gains occurring with additional time in treatment. That is, patients enrolled for several months are, in the aggregate, "roughly" comparable clinically to those enrolled for several years.)

Two limited forms of data entry verification were done. One involved visually checking a 10% random sample of data-entered cases selected for analysis (n = 560, see below), with their associated data collection sheets, by a person not involved in the original data entry. Errors of commission and omission were both less than 1 percent. Corrections were made to the appropriate records. The second type of verification involved asking providers to recompile and submit data on the number of positive urine toxicologies for selected patients who, it seemed, had very high values. In *every* instance, the newly compiled results yielded a value for positives in agreement with that on the original data collection sheet.

Because of uncertainty regarding the completeness of printouts of discharged patients, and the data on eligible patients not on the original list, we decided to develop a 10% stratified random sample of patients from the available data. Every PRU (n = 116) in New York State's MMT system contributed at least one patient. Ten percent of patients within every PRU were selected. This resulted in a sample size of 560 individuals. The contrast group numbered 7,250.

RESULTS

The Ten-Year Patient Population

The CDS computer run in August 1996 yielded an n of 6,244 active patients who met the criterion of 10 years or more in treatment, with an interruption of no more than 90 days. The total MMT population in New York State as of the end of August 1996 was 35,006 (this excluded MMT correctional patients enrolled in the Key Extended Entry Program (KEEP) and patients in methadone-to-abstinence or MTA programs). Thus, the ten-year patients comprised about 18% of the MMT population.

Descriptive statistics on selected outcome measures for the 10-year patients and the contrast group, where available, are presented below.

1. Arrests

The data collection form asked for information on the number of arrests in the past six months for each individual in the 10-year group (i.e., from February 1996 through July 1996). Tables 1 and 2 present the findings on average number of arrests for the 10-year patients and for contrast group patients, and the number in each group who were arrested or not.

The results in both tables show a very large advantage in favor of the 10YR patients, i.e., the average number of arrests and the percentage who were arrested, were both very much lower for the 10-year than for the contrast patients. These results are consistent with previous studies showing low arrest and incarceration rates among active MMT patients (1).

TABLE 1

Number of Arrests in the Last Six Months

	n	Average
10-year patients (total number = 356)	13	0.036
Contrast patients (total number = 6,842)	3,868	0.565

$p < 0.0001$

TABLE 2

Number of Patients Arrested or Not Arrested in the Last Six Months

	Arrested		Not Arrested	
	n	%	n	%
10-year patients (total number = 353)	5	1.4	348	98.6
Contrast patients (total number = 4,887)	1,380	28.2	3,507	71.8

$p < 0.00001$

2. Hospitalization for Non-detoxification Services

Tables 3 and 4 present findings on hospitalization in the past six months for the 10YR and contrast patients. The contrast group had a higher rate of hospitalization than the patients in the 10YR group, and more than twice as many hospitalized days. A previous OASAS report (1997) showed a decline in days hospitalized from a year before admission to a year after discharge, for all non-MMT programs.

The expectation for MMT patients, as for other AOD treatment clients, is that enrollment in treatment brings attention to previously

TABLE 3

Number of Days Hospitalized for Non-detoxification Services in the Past Six Months

	n	Mean
10-year patients (total number = 378)	547	1.45 days
Contrast patients (total number = 6,842)	20,222	2.96 days

$p < 0.05$

TABLE 4

Hospitalized or Not for Non-detoxification Services in the Past Six Months

	Hospitalized		Not Hospitalized	
	n	%	n	%
10-year patients (total number = 446)	48	10.8	398	89.2
Contrast patients (total number = 7,250)	1,079	14.9	6,171	85.1

$p < 0.0001$

neglected medical problems and so may result in increased hospitalization, in the short run. Continued enrollment should result in fewer medical problems requiring hospitalization, though the HIV/AIDS and hepatitis C epidemics are affecting older patients who may require periodic hospitalization independent of the length of their treatment tenure.

The findings for the 10-year patients are consistent with this scenario. The difference between the 10-year and contrast group patients in the rate of hospitalization was statistically significant; however, it was not large in absolute terms and reinforces the suggestions above as well as anecdotal observations about the serious medical problems affecting some long-term patients.

3. Emergency Room Episodes

Inappropriate use of the emergency room is a significant contributor to health care cost increases, and a decline in ER episodes would be desirable from a cost control standpoint. At the same time, some MMT patients have serious medical problems (e.g., AIDS, hepatitis C) which may become acute and require emergency room attention (Table 5). The findings here show that the rate of emergency room episodes is lower for the 10-year patients but not significantly so. Further, while the mean number of ER episodes is also lower among the 10-year group than among the contrast group of patients, the 0.2 episode per 10-year patient is not significantly lower than the 0.3 episode per contrast group patient (Table 6).

4. Employment

Employment has been a traditional measure of an AOD treatment outcome, and maintaining or improving patients' level of vocational involvement reflects treatment effectiveness. The findings here only show status at a point in time, i.e., employment status for the 10-year patients in August 1996, and for the contrast group, at the time of discharge, for discharges during the first six months of 1996 (Table 7).

The employment status categories for the contrast group were derived from the OASAS discharge form (the PAS 45), and include any employment; being unemployed; and a variety of not-in-the-labor-force statuses, including being disabled. About 90% of the employed patients were employed full time, while about 10% where employed part time.

A Chi-Square test was done to determine whether the percentages in the various employment status categories for the 10-year and contrast patients were significantly different. The result shows that twice the percentage of 10-year patients were working, compared to contrast group patients, and almost twice as many contrast group patients were unemployed. Consistent with the employment findings, data on principal source of payment for treatment showed more than twice as many 10-year patients as contrast patients who were self-paying, 34.0% versus 16.5% (Chi-square = 717.8, $p < 0.00001$). Further, while the treatment of significantly fewer 10-year than contrast patients was paid by Medicaid, 56.2% versus 63.9% ($p < .001$), a majority of 10-year patients were nevertheless supported by Medicaid and/or other benefits.

Illustrative of the diversity among the 10-year patients, nearly twice as many of them were classified as disabled than were contrast

TABLE 6

Number of Emergency Room Episodes in the Past Six Months

	n	Mean
10-year patients (total number = 375)	75	0.20
Contrast patients (total number = 6,842)	2,060	0.30

p = 0.26

TABLE 5

Any Emergency Room Episodes in the Last Six Months

	Emergency Room Episodes		No Emergency Room Episodes	
	n	%	n	%
10-year patients	48	9.7	446	90.3
Contrast patients	921	12.7	6,329	87.3

p = 0.20

TABLE 7

Employment Status for 10YR and Contemporary Contrast Group Patients

Group	Status	n	%
10-year patients	Employed	182	38.7
	Unemployed	126	26.8
	Not in labor force **	22	1.0
	Not in labor force — "other"	47	4.7
	Not in labor force — Disabled	93	19.8
Total number		470	
Contrast patient	Employed	1,289	18.8
	Unemployed	3,378	49.4
	Not in labor force **	481	7.0
	Not in labor force — "other"	940	13.7
	Not in labor force — Disabled	755	11.0
Total number		6,843	

$p < 0.00001$

** Employment status at discharge categories 7, 8, 9, 11 and 12 include "student," "retired." "Disabled" is also a not-in-the-labor force category; it was presented separately because of its treatment and policy implications.

Employment status categories
7 = not in labor force — student
8 = not in labor force — retired
9 = not in labor force — inmate
10 = not in labor force — disabled
11 = not in labor force — child-caring issues
12 = not in labor force — in training

group patients. These findings support clinical observations of serious medical problems and handicap conditions among some long-term patients.

Finally, these data do not address the origin(s) of the difference in employment status between the 10-year and contrast group patients. One possible source is that the two groups differed in employment prospects before admission; another, that treatment contributed to a favorable vocational outcome.

5. Drug and Alcohol Use

The primary goal of MMT is to reduce or eliminate the use of illicit opiates; nonopiate drug and alcohol use are addressed in the course of treatment, but MMT has a specific pharmacological efficacy that does not extend to the latter substance categories. Previous studies show major reductions in illicit opiate use, but also, smaller reductions in non-opiate use (1).

The main measure available for assessing illicit drug use is the finding of positive urine sample, indicative of use of illicit drugs. For this project, these data were compiled from urinalysis reports for the six months prior to the data collection request. The results show that more than 60% of the 10-year patients had no positive toxicologies for illicit drugs in the past six months and 18% of the patients had up to three positive toxicologies. On the other hand, 14% of the patients had seven or more positive urinalyses (Table 8).

Usual urine testing frequency in MMT programs is once per month, although it can be more frequent to determine if a patient is adhering to a contract or agreement to stop using an illicit drug(s). More frequent testing may also be done occasionally at a patient's request, to provide external confirmation of abstinence. In fact, 5.4% of the patients had at least 16 positive toxicologies and we were concerned about the validity of these findings. As a result, requests were made to recompile the urinalysis findings. In every instance, the number of positive urinalyses was confirmed, and in every case it involved a positive for cocaine; in two instances, there was also a positive for illicit opiates.

Thus, the great majority of long-term patients showed no-to-minimal illicit drug use, while a noticeable minority showed persistent, and some, a seemingly intractable use of cocaine. As for problematic use of alcohol, its frequency as a current problem was reported for only 5.5 percent of the sample (see Table 9).

6. Methadone Dose

Dosage data were reported for most of the 10-year patients (525 of 560). In line with best practice recommendations and research (4, 5), more than half the patients received doses greater than 70 mg. The average dose was 64.2 mg (standard deviation ± 27.7 mg). However, about a quarter of the patients received doses of 40 mg or less. While such doses are too low for

TABLE 8

Number of Positive Urinalyses for Illicit Drugs in the Last Six Months for 10YR Patients

Number of Positive Samples	n	%
0	276	61.9
1–3	80	17.9
4–6	29	6.5
7–15	37	8.3
≥ 16	24	5.4
Total number	446	

114 patients had missing data (The data collection form did not indicate the number of urine samples which tested positive.)

TABLE 9
Percentage of 10-year Patients Considered to Have an Alcohol Problem in the Past Six Months

Had an Alcohol Problem	n	%
Yes	31	5.9
No	497	64.1
Total number	528	

32 patients had missing data (The data on a patient's alcohol problem status was not indicated on the data collection form submitted by the patient's counselor.)

optimum results (3), more information will be needed to determine whether clinically deficient practices were involved. Some patients may function satisfactorily at such doses; further, some patients may have been in clinically supervised withdrawal.

Summary and Conclusions

This study was conducted to determine the size of the MMT population in New York State with 10 or more years of continuous treatment (which could include one interruption up to 90 days) and their treatment status and selected outcomes. Some of the outcome data for the 10-year patients was compared to results for the population of methadone patients who had three months to five years of treatment and who were discharged during the first half of 1996. These patients provided a contemporary contrast group.

MMT is designed for indefinitely long periods of enrollment, to enable opiate addicts to function normally. Discharges from MMT are often under unfavorable conditions, e.g., relapse, arrest, compliance violations, negatively biasing comparisons between discharged and active patients (6). Thus, active patients, especially those with extended tenures such as the 10-year patients in this study, should exhibit superior outcomes.

In fact, the results support this expectation overall, though some of the differences between the 10-year and contrast group patients were small. One of the largest differences was for arrests. For example, the arrest rate for the 10-year patients was a negligible 1.4%, while the rate for the contrast group patients was twenty times as large. The 10-year patients had lower rates of hospitalization and fewer days hospitalized, and fewer of them used emergency room services. More than double the number of 10-year than contrast group patients were employed, and a similar relationship was observed regarding primary source of payment for treatment, i.e., over twice as many 10-year patients paid toward their own treatment as did contrast group patients.

While the findings were consistent with expectation, namely, that long-tenured MMT patients would exhibit better outcomes than discharged patients, it is the case that many 10-year patients showed dependency on benefits, and a noteworthy minority were classified as disabled. The low rate of self-sufficiency among long-term patients observed here indicates that there is significant room for improvement in the MMT system. OASAS's very recent efforts to increase vocational-educational resources is an attempt to address this problem; external pressures exerted by welfare reform are also fostering a greater focus on patient self-sufficiency and employment. Further, anecdotal reports of medical problems which limit patient functioning need to be systematically explored.

The results for the 10-year group are of special interest because of the paucity of data on patients with such extended treatment tenures. The findings on hospitalization, emergency room use, and disability among the 10-year and contrast group patients suggest that long-term patients are very distinct populations, with different levels of rehabilitative accomplishment and ongoing needs. These remain to be characterized in further research. The 10-year MMT population is a heterogeneous group demonstrating worthy outcomes. A major component includes patients with serious medical and social problems, for whom MMT may be an essential anchor. Additional rehabilitative efforts are required to address the issues of low productivity and various remaining medical and social obstacles.

The results have important implications for policy concerning those 10-year patients whose status is clinically tolerable-to-marginal, but who evidence no movement toward self-sufficiency. Many such patients persist in using crack/cocaine and may engage in illicit activity to purchase it.. However, a growing concern among MMT clinic staff with the transmission of such infectious diseases as HIV/AIDS has led staff to retain such patients. In effect, the MMT treatment policy and provider communities have tacitly decided in favor of patient and public health with some sacrifice of more traditional concerns.

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Leaving Methadone Treatment:

Lessons Learned, Lessons Forgotten, Lessons Ignored

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Abstract

Despite the demonstrated benefits of methadone maintenance, there have been concerns about the ethics, necessity and expense of maintaining addicts on methadone indefinitely. The inability of many patients to achieve normative levels of psychosocial functioning with methadone, combined with widely held attitudes favoring drug abstinence over replacement medication, has led to attempts to promote time-limited methadone treatment. This paper reviews the published research literature on post-discharge outcomes of patients exiting from extended methadone detoxification, "abstinence-oriented" methadone programs, and regular methadone maintenance programs. Virtually all of these studies document high rates of relapse to opioid use after methadone treatment is discontinued. Most of the patients studied left treatment without meeting clinical criteria for detoxification, although high relapse rates were also reported for patients who completed this program. The detrimental consequences of leaving methadone treatment are dramatically indicated by greatly increased death rates following discharge. Until more is learned about how to improve post-detoxification outcomes for methadone patients, treatment providers and regulatory/funding agencies should be very cautious about imposing disincentives and structural barriers that discourage or impede long-term opiate replacement therapy.

Key Words: Methadone maintenance, drug abstinence, post-discharge outcomes.

Introduction

PREVIOUS RESEARCH HAS SHOWN that outcomes have generally been poor after short-term heroin/opiate detoxification; large percentages of detoxified addicts rapidly relapse to heroin/opiate use (1). The availability of naltrexone, an opiate antagonist, to extend opiate abstinence after detoxification has not altered this verdict; few persons to whom naltrexone was administered continue to take it for more than a month or two (2, 3). However, methadone maintenance with adequate dosing (4, 5) has been shown to eliminate or dramatically reduce patients' heroin use and improve their psychosocial functioning (6–9).

Nevertheless, even from the outset, there have been concerns about the ethics, wisdom, necessity and expense of maintaining addicts on an opiate replacement indefinitely, possibly for the rest of their lives (10, 11). The depiction of irreversible neurological and metabolic changes in long-term opiate addicts remains a credible hypothesis, not acceptable by all, to help explain the remarkable persistence of opiate misuse by individuals (12). If methadone-maintained patients generally achieved a normative level of psychosocial functioning, surely there would be less criticism of the modality, but this goal has not been achieved. Addicts usually improve substantially after entering methadone treatment, particularly by eliminating or reducing opiate use, drug-injection-related health risk habits and criminal activity. However, they often continue to misuse substances other than opioids (a pattern usually predating treatment) and most remain economically dependent. An excellent comprehensive review of methadone treatment issues can be found in Ward et al. (9).

The mixed outcomes of methadone maintenance, at least as it is traditionally administered and delivered, have led to a curious conclusion in some quarters. Because many patients remain economically dependent,

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some say that methadone maintenance fosters economic dependency. Because many patients misuse substances other than opiates, some say that methadone maintenance precipitates the use of other illegal substances, such as cocaine, in place of opiates (13). Comparisons of employment and polysubstance abuse before and after entry into treatment, and changes during treatment, generally belie these assertions (6, 14), but these facts have not been sufficiently reported to the public and policymakers. Thus, there have been renewed calls for restricting the length of methadone treatment.

Although the attempt by Mayor Rudolph Giuliani of New York City to limit methadone treatment may be the latest and most public (15), other less visible, more subtle and perhaps more effective policies and actions with the identical objective have been in place nationally and internationally for some time. These include: actual limitations on the length of treatment; reduction or elimination of public subsidies for methadone maintenance; "low dose" methadone policies and practices, due to either state regulations or individual program practices; rules prohibiting or discouraging the expansion of medical maintenance; poor physical clinic facilities; marginally trained or demoralized staff; and a variety of disincentives for methadone patients to improve themselves, such as overly stringent requirements for admission to vocational rehabilitation programs (4, 11, 16–19). All these factors contribute to patients leaving methadone treatment, so that the number of "long-term" stabilized patients, historically never very large in any event (20), seems to be decreasing. Thus, nationally one-half of admissions to methadone treatment leave within one year (21), and in Texas three-quarters leave within a year (22).

Consequently this paper will revisit the question, "What are the observed consequences of patients leaving methadone maintenance?" Is it ever wise to encourage this move, and if so, for which patients, or under what circumstances, might it be acceptable to do so? In particular, how numerous and successful are "planned" or "therapeutic" long-term detoxifications from methadone treatment? Can we learn anything from the history of research concerning this important issue?

Methods

The published literature since 1966 was screened using major automated bibliographic databases (MEDLINE, PsychInfo) to identify relevant published articles. Relevant research published as books was identified by citations in articles and the authors' knowledge of the methadone field; very little such research is initially or solely published in book form.

Three types of follow-up studies are reviewed:

1. Studies of patients exiting from time-limited methadone programs (i.e., "methadone to abstinence" programs or "abstinence-oriented" methadone programs).
2. Studies of discharged patients who began a planned (clinically approved or "therapeutic") detoxification from a methadone maintenance program. We rely on Milby's comprehensive review for such studies through 1985, only adding some details and commentaries on certain major studies included in that review (23).
3. Studies of patients leaving methadone maintenance programs for diverse or unspecified reasons. These studies generally do not indicate how many patients, if any, underwent detoxification before discharge. They involve either the discharged patients only or they compare discharged patients with those who remained in treatment.

The primary outcome measure examined is whether relapse to regular or periodic opiate use occurs within a one-year post-treatment period. However, because one-year outcomes are not always explicitly presented in the short-term studies, those with somewhat shorter (e.g., six months), longer (e.g., two years) or variable post-treatment follow-up periods are included. The presence of opiate use at exit from treatment or a return to methadone treatment is assumed to indicate post-treatment use as well. Lastly, outcomes known to be closely related to opiate use, especially mortality and crime, are presented as plausible consequences of extensive opiate use after treatment discharge.

Long-term patient outcomes (usually five years or longer) generally are not analyzed, because these outcomes may be affected by many factors which might not be evident during the index methadone treatment episode. Most such studies have not been designed to examine the different contributions to outcomes. Also, short-term outcomes should generally be superior to long-term, in the absence of additional intervention or factors such as maturation. If abstinence cannot even be achieved before leaving the program, or if immediate relapse to opiate use occurs after leaving, then there would seem to be little prospect for more positive long-term outcomes.

Results

1. Outcomes of Time-Limited Methadone Programs

Only four studies, all published in the 1990s, assessing outcomes of discharge from methadone to abstinence or other time-limited methadone programs, were identified (Table 1).

Banys et al. (24) established and evaluated a long-term methadone detoxification program providing intensive therapeutic support to help the addict achieve abstinence. Patients volunteered for the program; they reportedly were attracted because the program was easy to enter and focused on gradually tapering off methadone, thereby countering their fear of long-term dependence on methadone. Nevertheless, a majority of those who remained until the final month did not succeed in ceasing opiate use. Overall, only 27% of patients who entered the detoxification program successfully completed it. The 80-mg group did very well during the stabilization phase — the percent of opiate-positive patients declined steadily to 31% by weeks 11 – 14 — but then increased to 62% during the mandatory taper by weeks 23 – 26.

Strain et al. (25) reported difficulty in retaining patients in their low-dose, methadone-to-abstinence trial. Methadone dose level during maintenance was not predictive of outcome; the largest reductions in drug use at follow-up occurred for subjects who had reentered methadone treatment.

Two evaluations of time-limited methadone were conducted in Australia. Capelhorn (26) found that patients discharged from an abstinence-oriented clinic were not less likely to relapse and return to treatment than those discharged from a maintenance-oriented clinic. Bell et al. (27) reported a significantly higher rate of opiate-positive urinalysis (25%) at a methadone clinic oriented to time-limited treatment and abstinence from all drugs, as compared with a methadone clinic oriented to long-term maintenance (18%); this seemed to be due to the lower average doses in the abstinence-oriented clinic.

2. Outcomes of Planned Detoxification from Methadone Treatment

Milby (23) examined 14 methadone maintenance detoxification studies that had been conducted from 1970 through 1985. Eleven of these studies included patients who met criteria for rehabilitation before detoxification. Patients qualifying for rehabilitation were those who met the study clinic's "rehabilitation criteria" or who were identified by staff as "most likely to succeed." Patients qualifying for abstinence after detoxification were those who were not using heroin and were not returning to methadone treatment. All patients had been in methadone maintenance for at least six months before undergoing detoxification. Successful detoxification was defined as achieving a zero methadone dose. Uncontacted patients were coded as not abstinent, although inspection of certain studies reveals some ambiguity about the interpretation of "uncontacted."

Based on Milby's tables, we calculated the 6 – 12 month abstinence rates for rehabilitated Methadone Maintenance Treatment Program (MMTP) patients who successfully completed detoxification. Among the 768 rehabilitated patients who entered a detoxification protocol, 33% were not using heroin 6 – 12 months later.

Many of the studies reviewed by Milby lack complete and consistent data. A closer inspection of studies reporting putatively better outcomes suggests that the 33% post-discharge abstinence rate may, in fact, be an overestimate and that patients who completed detoxification represented less than half the "rehabilitated" patients who began a planned detoxification protocol.

For example, Milby's review indicates a 6 – 12 month abstinence rate of 63% (59/94) for those who completed detoxification in Kaufman's evaluation of a long-term, residential methadone detoxification program based on therapeutic community principles (28). Actually, no estimate of post-discharge abstinence is possible for this study, since no follow-up interviews were done and "staying off methadone" is not equivalent to abstinence. Kaufman does state that 37% (20/54) of those detoxified patients who had left the program (40 others who were detoxified apparently remained in residence) had re-entered methadone treatment, indicating relapse; drug use for the remaining 34 patients was unknown.

One of the highest abstinence results for planned detoxification in Milby's review was that reported by Cushman (10), who indicated that 46% of such successfully detoxified patients remained narcotic-free for an average of 2.4 years after discharge (partly verified by

TABLE 1

Outcomes for Patients Leaving Time-Limited Methadone Programs and/or Receiving Planned Detoxification from Methadone

Study	Locale/Clinic	Method	Results	Comments
Banys et al. [a] (24)	San Francisco Veterans Admin. "Methadone Transition Treatment" (MTT)	38 subjects randomly assigned to either 80 mg or 40 mg methadone dose for 3 months followed by 3-month straight line taper to abstinence. Program included intensive psychological services to support detoxification.	Two-thirds of patients were retained until the final 2 weeks. Among those remaining in the final month, approx. 59% had opiate-positive urines. Among the 80-mg group, the percent of opioid-positive patients declined during the stabilization phase and increased during the taper phase.	The post-discharge follow-up mentioned in the paper has not appeared in the literature.
Bell et al. [a] (27)	MMTs in Australia	191 patients in an abstinence-oriented clinic and 61 patients in long-term maintenance-oriented clinic. Outcomes measured by urinalysis during first 18 months.	The abstinence-oriented clinic had a higher rate of opiate-positive urinalysis (24.2%) than the maintenance-oriented clinic (18.7), which was shown to be due to lower average medication dosage in the former, i.e., positive urines increased when methadone tapering began.	Penalties for drug use in abstinence-oriented clinic might have increased urine specimen falsification there.
Capelhorn [a] (26)	MMTPs, Sydney, Australia	152 patients admitted to an abstinence-oriented clinic (#1) and 75 admitted to maintenance-oriented clinic (#2), determined by site closest to home, were followed up a mean of 5 years after admission.	By the time of follow-up, 68% of those discharged from clinic #1 vs. 56% discharged from clinic #2 had returned to treatment (n.s.). The longer patients had stayed in abstinence-oriented treatment (#1), the more likely they were to relapse after discharge and return to maintenance (sig.).	Length of stay finding is unusual.
Sorensen et al. [b] (30)	MMTPs in San Francisco	58 patients in 3 clinics received up to 6 months of enriched support for withdrawal from methadone vs. 56 patients in 3 clinics as a comparison group. All patients wanted to withdraw and met criteria predictive of success. Follow-up 3 months after study termination.	Withdrawn from methadone at study termination — 29% of experimental vs. 20% of controls (n.s.). No sig. difference between groups in severity of drug problems, from study entry to 3-month follow-up.	Percentage relapsing to opiate use at follow-up is not reported.
Strain et al. [a] (25)	Baltimore short-term MMTP	Double-blind, random assignment of 171 newly admitted addicts to one of the 3 doses of methadone – 50 mg, 20 mg, 0 mg – for the stable dosing phase of weeks 6 – 20. Uniform detoxification and discharge by week 26 and post-discharge follow-up at week 36.	Fifty-four percent dropped out of treatment during stable dosing. All groups reported significant reductions in heroin and cocaine use between admission and follow-up. Those who re-entered treatment at follow-up (35% of sample) reported significantly greater reductions in drug use than those not re-entering treatment. Drug use outcomes at follow-up identical for all three dosing groups.	No biological validation of drug use. Numbers dropping out during detoxification phase not stated. Taking self-reports at face value, apparently active dosing did not improve post-discharge outcomes.

[a] Time-limited methadone programs, [b] Planned detoxifications from methadone

urinalysis at follow-up). However, only 63% of patients beginning planned detoxification completed the program successfully, resulting in 29% of the original group remaining narcotic-free. Finally, only 27% of 513 patients treated in the program during an 11-year period (excluding transfers and deaths) met program criteria for planned detoxification.

A similar study by Stimmel et al. (29) reported that, of 335 patients detoxified, only 17% were considered to have "completed treatment" by the program staff. This small group did well, with 83% showing no evidence of narcotics use, as compared with 16% of those detoxified for other reasons (including voluntarily discontinuing treatment), by the time of an average 26-month post-discharge follow-up. One limitation of this study is that the assessment of treatment completion was made retrospectively by staff, who may have been influenced by subsequent contacts with previously detoxified patients, i.e., "a person was considered abstinent only if he had been seen at periodic intervals by treatment staff with neither positive signs of opiate abuse nor positive urinalysis for narcotics being found."

Lowinson et al. (20) identified about 10% (228/2814) of patients in a large methadone program as meeting criteria for planned detoxification. These patients were: in treatment for at least one year; drug or alcohol-free for at least six months; and employed, in school, or functioning as homemakers for at least six months. Of 63 patients who accepted and completed detoxification (others were still in the program) and were followed for at least three months, 22% had verified drug abstinence from illicit drugs. Although the program offered flexible, continuing counseling support, 64% did not return after detoxification, giving poor reasons, or were lost to contact. The remaining 14% had returned to methadone maintenance. Thus, even in this small group especially selected for their good prognosis and motivation to detoxify, outcomes seemed disappointing.

The only published study of planned detoxification from methadone appearing since Milby's review, that of Sorensen et al. (30), reported difficulty in detoxifying even motivated patients (see Table 1). Patients who expressed interest in withdrawing from methadone and who met predictive criteria for success (i.e., recommended by counselor, in treatment for at least six months, no opiate-positive urine for the past three months) were assigned either to an array of supportive psychosocial services or to a comparison group (apparently the clinic's usual detoxification protocol). Only 27% of the sample tapered to zero milligrams, and there was no significant difference in completion rates between the two study groups.

3. **Outcomes for Patients Leaving Methadone Maintenance for Diverse or Unspecified Reasons**

Table 2 presents the findings of short-term follow-up studies (about 1 – 2 years) which meet the inclusion criteria for the review. [Several additional studies (31, 32) are cited in Milby's review]. The studies are very diverse and cover about 35 years of experience with methadone maintenance. Nevertheless, the results are very similar — in every study reporting the pertinent data, a majority (usually a large majority) of discharged patients returned to treatment shortly after leaving treatment or, if they did not return to treatment, were using opiates, were in trouble with the law and/or had high death rates. In studies which compared discharged patients with patients who stayed in treatment, patients who had left methadone treatment had poorer outcomes.

Few of the short-term follow-up studies of methadone patients reviewed [Ball and Ross (7) and Zanis et al. (33) are the exceptions] provide information on reasons for exit or discharge, although this information might help explain differences in outcomes (9). Several of the long-term outcome studies, however, do provide such data. ("Completing treatment" is generally defined as planned discharge or discharge with staff assent.) Stimmel et al. (31) reported better outcomes among patients who completed treatment than among patients who exited for other reasons, and concluded that length of treatment per se did not explain the better outcomes.

Dole and Joseph (32) reported on 848 methadone patients who were discharged from treatment. Only 72 (8%) were "doing well" at post-treatment follow-up, while this held true for only 2% of 217 dropouts and 1% of the 356 who were administratively discharged for behavior problems, alcoholism and intractable drug use. In this study, "doing well" meant that subjects were abstaining from heroin, were not abusing alcohol or non-opiate drugs, and had not been rearrested. Duration of street addiction, length of time in treatment, problems in treatment, type of discharge (favorable or

TABLE 2

Outcomes for Patients Leaving Methadone Maintenance Programs

Study	Locale/Clinic	Method	Results	Comments
Anglin et al. (65)	San Diego, CA	2-year follow-up of 331 MMTP patients after their treatment in a publicly financed program was terminated.	52% transferred to private methadone and other programs. 59% used heroin during follow-up period. Patients who did not transfer reported more narcotic use, property crime, drug dealing and incarceration.	Urinalysis used to help measure drug use.
Ball & Ross (7)	Six MMTPs in New York City, Philadelphia, Baltimore	Among a sample of 607 MMTP patients, 38% left treatment within 1 year (Chapter implies that funding limitations restricted follow-up of discharged patients to 107).	Within 1 year, 82% of the 107 discharged patients reported they had relapsed to IV drug use. 22% of discharged patients were "treatment completers" (they completed their detoxification and were identified by staff as "ready to become drug free"). Within 1 year after discharge 30% had returned to drug abuse treatment, 39% had relapsed to IV drug use and were not in treatment, and 30% were identified as "cured" (not in treatment and reported no IV drug use).	Since drug use is restricted to IV use, the percent reported as "cured" likely underestimates dropouts who returned to drug use. Self-reported drug use only.
Gossop et al. (66)	National Treatment Outcome Research Study (NTORS) in the United Kingdom	Included 458 patients in methadone maintenance clinics and 209 in methadone reduction programs who were followed up 6 months after treatment admission during 1995.	Approx. 50–60% of methadone patients who left the index treatment had re-entered some form of treatment within the 6-month period.	No comparison of drug use between subjects in vs. out of methadone treatment at 6 months.
Gossop et al. (67)	MMTP in United Kingdom	80 patients were followed up 6 months after discharge from methadone treatment.	71% reported using opiates within the first 6 weeks after discharge; 55% were using opiates at 6 months.	Self-reported drug use only.
Hubbard et al. (68)	National Study of Drug Abuse Treatment Outcomes (DATOS)	727 MMTP patients who were admitted during 1991–1993 and were followed up either (a) one year after discharge from the index treatment, or (b) about 2 years after admission if they remained in the index treatment. The outcome measures were self-reported occurrence of regular (weekly or greater) substance use during past year.	Those still in the index treatment 2 years after admission used heroin at one-third the rate of those who stayed six months or more, but were not in the index treatment during the past year (Table 5). (The corresponding comparison for cocaine use was unclear.)	No explicit statistical significance test was available for the result cited, but it is likely to be significant. Some patients not remaining in the index treatment entered subsequent treatment, but this was not included in the multivariate analysis. Self-reported drug use only.
Hubbard et al. (6)	National Treatment Outcomes Prospective Study (TOPS)	835 patients who were admitted to methadone in 1979–1981 and were followed up (a) one year after discharge from the index treatment, or (b) about 3–5 years after	Those still in the index treatment at follow-up (n=183) used heroin at one-half the rate of those who had stayed one year or more and were discharged (n=137) (the corresponding comparison for cocaine use was unclear). 58% of patients discharged from the index	No explicit statistical significance test was available for the result cited, but it is likely to be significant. Some patients not remaining in the index treatment entered subsequent

TABLE 2
Continued

Study	Locale/Clinic	Method	Results	Comments
		admission if they remained in the index treatment. The outcome measures were the self-reported occurrence of regular (weekly or greater) substance use during the past year.	treatment returned to treatment in the first year after discharge; premably all had returned to heroin use, although only 17% of discharged patients reported regular heroin use during the post-discharge year.	treatment, but this was not included in the multivariate analysis. Self-reported drug use only.
Joseph et al. (41); Joseph & Appel (42)	All MMTPs in New York City	Samples of patients admitted during 1966–1967 (n=648) and 1972 (n=897), followed-up in 1976.	Death rate during treatment: 15.2/1000 person-years Death rate, first month after discharge: 90.0 Death rate, first year after discharge: 37.4 Death rate, entire post-discharge period: 35.2 Drug-related death rate during treatment: 6.0 Drug-related death rate, entire post-discharge period: 24.0 Leaving treatment is associated with greatly increased death rates, even in short-term.	Pre-AIDS era.
Kosten et al. (69)	MMTP, New Haven, CT	79 methadone patients admitted in 1977–1978, who completed at least 6 months of treatment and then left treatment for at least 6 months during a 30-month post-admission follow-up period.	Use of opioids significantly decreased after entering treatment and significantly increased in the 6 months after leaving treatment. For those re-entering treatment and remaining at least 6 months (n=44), opioid use again significantly decreased. Employment also significantly decreased after leaving treatment. There were no significant changes in cocaine use.	Self-reports of drug use only. Reasons for leaving treatment and number undergoing detoxification not stated.
Maddux & Desmond (70)	Texas MMTP	610 enrollees were followed up for 1 year. Pre-post 30-day comparisons were made between out-of-treatment subjects and in-treatment subjects.	At 1-year follow-up, 47% had continuously remained in MMT, 5% had been discharged and returned to MMT and 48% were no longer in MMT. 35% of the out-of-treatment sample was incarcerated during the 1-year follow-up anniversary month. Compared with the out-of-treatment subjects who were not incarcerated (183), in-treatment subjects reported fewer days of IV drug use in last 30; (3.7 vs. 19.9) and crime (1.5 vs. 15.2).	Drug use is based on self-report and non-injecting drug use was not reported. Although percent of subjects using drugs was not reported, the high frequency of days using drugs suggests that most out-of-treatment subjects were injecting.
Maddux & McDonald (71)	San Francisco MMTP	One-year follow-up from date of 100 patients enrollment.	26 Subjects left MMT during the 1-year follow-up. 11.5% (3/26) of the MMT discharges were identified as abstinent; the remaining 23 subjects had returned to MMT (4), were institutionalized (10), using heroin (4), dead (1) or had an unknown status (4).	Self-reported drug use only. Heroin use at 1 year for subjects still in MMT was not reported.

TABLE 2
Continued

Study	Locale/Clinic	Method	Results	Comments
			Employment at 1-year follow-up was 81% for MMT subjects and 11% for subjects not in MMT.	
McGlothin & Anglin (72)	California MMTPs	99 patients who were discharged from methadone treatment when their Bakersfield clinic closed and 88 patients who were in treatment in nearby Tulare. Both groups followed up for 2 years after the date of the Bakersfield closure. During those years, the Bakersfield group spent 8% of non-incarcerated time in treatment vs. 73% for Tulare group.	Bakersfield group: 55% reported periods of daily heroin using during follow-up period and 30% of those not incarcerated tested opiate-positive at 2-year interview. Tulare group: Respective figures were 32% and 16%.	Consequences of involuntary termination of treatment might be less severe with more counseling preparation or access to alternatives
Perkins and Bloch (35)	MMTP in New York City	60 patients were followed up and located a mean of 2 1/2 years after discharge. Their mean length of stay was about 8 months.	10% had died and 57% had been or were currently hospitalized for physical/mental conditions or detoxification. Of the 38 non-institutionalized or non-incarcerated respondents, 76% admitted current heroin use and 95% admitted some current drug or abusive alcohol use. Subsequent attempts at detoxification had been made by 52% (31/60) of these dropouts.	
Rosenbaum, Murphy & Beck (73)	California MMTP	25 patients who were detoxified from treatment because they would not or could not pay for treatment when their program switched from no-cost to pay-for-service.	83% reported using heroin after detoxifying.	Self-reported drug use only.
Zanis et al. (33)	Philadelphia VA MMTP	Status of 94/110 discharged methadone patients determined 1 year after discharge. 13/110 (12%) were identified as treatment completers.	10% died, 39% re-enrolled in treatment, 44% eligible for treatment (presumably using opiates) and 7% did not require treatment (presumably abstinent).	Urine specimens taken to help establish abstinence.
Zanis & Woody (43)	Philadelphia VA MMTP	507 patients: 1-year follow-up of mortality rates.	8.2% (9/110) of discharged patients died vs. 1% (4/397) of non-discharged patients. Six of the discharged sample and none of the non-discharged sample died of heroin overdose.	Discharged patients represented treatment failures since most had voluntarily dropped out or were administratively discharged for violating clinic rules. Results suggest that

TABLE 2
Continued

Study	Locale/Clinic	Method	Results	Comments
				greater efforts should be placed on retaining the most problematic patients.

MMTPs, MMT – Methadone Maintenance Treatment Programs; VA – Veterans Administration

unfavorable) and employment status were associated with post-treatment outcomes. Patients who relapsed to daily heroin use, when compared with patients who were not using heroin, had longer addiction histories (89 vs. 66 months), had shorter periods of treatment (17 vs. 47 months), were more likely to have problems while in treatment — behavior, drug abuse and arrests (76% vs. 37%), were less likely to have a favorable treatment discharge (11% vs. 81%) and were less likely to be employed at time of discharge (33% vs. 58%). Gender, ethnicity and education were not predictors of post-treatment outcomes.

A long-term outcome study found that relapse to opiate use occurred for 56% of the treatment completers, 76% of the dropouts, and 84% of those expelled (34). In a short-term outcome study, Ball and Ross (7) found that 30% of discharged treatment completers had not returned to treatment and reported no injecting drug use at one-year follow-up. Thus, even among small groups of treatment completers, only a minority appears to be opiate-free at follow-up.

Discussion

Outcome data reported for more than 30 methadone discharge studies reviewed in this paper lead to three main conclusions: (a) most patients who left methadone treatment were not identified by their clinic as therapeutically ready for discharge; (b) among patients who began a therapeutically planned discharge, most left methadone treatment before completing their detoxification; and (c) among patients who completed a therapeutically planned discharge, most relapsed to heroin use.

Difficulties in identifying patients suitable for detoxification and the likelihood of poor post-discharge outcomes were recognized soon after methadone treatment was established. One of the earliest concerns was raised by authors of a 1971 study (35) (see Table 2): "The post-discharge course of the 60 located heroin addicts who failed to continue in the methadone program appears to be in striking contrast to those who are reported as successfully maintained. Death, criminal-legal involvement, incarcerations and hospitalizations, and continued drug abuse patterns appear to be great risks for this group. . . . We believe this evidence suggests that intensified efforts to retain addicts may be needed in methadone programs. . . . We believe that measures that would make current programs more stringently regulated might have the effect of extruding [sic] more patients from the present system of care, and hence might consign more addicts to the street with a very poor prognosis for rehabilitation."

Cushman (10), who reported a relatively high post-discharge abstinence rate (46%) for patients who completed a planned detoxification, soberly concluded that "detoxification should not be a realistic goal for all patients who enter treatment," apparently countering the critics of methadone who were asserting that it should be. Further, "the number of patients who achieved an enduring narcotic-free state was low in relation to the number of patients treated and the duration of treatment . . . although there are some who achieve this laudable goal (enduring abstinence), there are many who fail even the process of detoxification and many who have a relapse to opioid use at various times during the completion of the detoxification process."

Another early investigator (10), whose study generated comparatively positive outcomes, wrote: "Even those persons who were highly motivated to be detoxified [voluntary detoxification] . . . [had] an impressive return to narcotic use. . . . Abstinence . . . does not appear to be a realistic goal for all, and . . . premature detoxification . . . with subsequent relapse to illicit heroin use, is prevalent. . . . It is important not to establish any specific criteria or regulations concerning the length of time that one should receive methadone therapy. Therapeutic plans must be individualized and detoxification, if considered appropriate, should be accomplished in a careful and well-planned manner that does not result in abrupt termination of program services."

Most of the reviewed studies are based on self-reports of drug use at follow-up. Research comparing biological indicators of drug use (urinalysis, hair analysis) with self-reports indicates that one-half or more of discharged drug-dependency-treatment clients who test positive for opiates or cocaine at follow-up fail to report use of these substances (36–40). Nevertheless, virtually all studies which address the issue document high rates of opiate use at follow-up, despite reliance on self-reporting!

The greatly increased death rate that occurs after patients leave treatment, which is primarily drug–related, is particularly noteworthy (41–43). This is supported by an earlier long-term mortality study in New York City (44), which reported a death rate of 7.6/1000 for patients while in treatment during 1964–1972 vs. 28.2/1000 while they were not in treatment. Considerable evidence was presented, showing that patients who leave methadone treatment have a high rate of relapse to opiate use during the year after treatment, that they use opiates at much higher rates than patients who remain in treatment, and that very few discharged patients have a planned discharge and gradual detoxification from methadone.

It could be argued that we ought to target more patients for therapeutically supported detoxification. However, as we have seen, early attempts within methadone maintenance programs (23) and more recent attempts in extended methadone detoxification programs (24–27, 30) have not been successful. In fact, given the finding cited in Table 1, that patients who were doing well on adequate methadone doses were likely to increase their heroin use when undergoing detoxification (24), programs should be very conservative when implementing a methadone-to-abstinence protocol.

In addition, relatively few patients today are able to meet accepted clinical criteria for planned methadone withdrawal (74); e.g., they do not have the requisite periods of abstinence from all drugs of abuse, they are not employed or otherwise financially stable, and they may have physical and mental health problems that render them highly vulnerable to relapse (7, 14, 45). The presence of treatment challenges faced by methadone programs is consistent with the finding that treatment completion as a reason for discharge from methadone maintenance treatment is becoming relatively infrequent. For example (46), in a multi-clinic sample in New York City, only 2% of discharges (13/634) during 1989–1993 were classified as having "completed goals." It has been observed that the crack and AIDS epidemics among drug users beginning in the mid-1980s have greatly increased the challenge of rehabilitating heroin addicts (47–49).

The persistence of problems while in treatment and the increase in problems after leaving treatment does not imply the absence of greatly improved or rehabilitated patients who remain in methadone maintenance. In the same multi-site study cited above (14), about 80% of new admissions to methadone programs started in or transitioned to a low heroin use group, and 50% started in or transitioned to a low cocaine/crack use group within three years of treatment.

In addition, there are important public health reasons, which this paper has not reviewed, to avoid early departures from methadone treatment. There is substantial evidence that participation in methadone treatment reduces the risk of HIV infection. Intravenous drug use, a prime vector of HIV transmission which historically has been strongly associated with heroin use, declines dramatically after entry to methadone maintenance (7, 49). Correspondingly, patients in treatment less than one year have a far greater HIV seroprevalence rate than those participating for longer periods (50, 51). Retention in methadone maintenance also has a protective effect against infection with hepatitis C (52). A complete current review of the public health benefits of methadone maintenance may be found in Ward et al. (9).

The paucity of planned discharges from methadone treatment does not seem attributable to the program itself. First, patients in maintenance-oriented programs have always had the right and opportunity to request planned, extended detoxification; there is no evidence that programs have placed barriers in the way of such requests. Second, research has documented widespread "abstinence-oriented" attitudes among methadone program staff, particularly the line staff who usually are a program's most salient contacts for patients.

For example, in a typical group of New York City clinics, one-quarter of the counselors were unfavorable to the concept of long-term methadone maintenance and another one-half displayed ambivalent attitudes (53). Other studies have documented the prevalence of similar abstinence-oriented attitudes among methadone staff (54 – 56). Thus, methadone staff appear to be generally favorable to facilitating patients' withdrawal from methadone.

One factor implicated in the reluctance of patients to request discharge is "detoxification phobia," attributed to a fear of opiate withdrawal symptoms (57), and the concomitant belief that withdrawal from methadone is more severe/protracted than from heroin (58, 59). This belief about methadone withdrawal may find some basis in self-detoxification experiences, since addicts typically leave methadone treatment without tapering off. If they cannot subsequently procure adequate (or use inadequate) amounts of heroin or other opiates, they will have unpleasant withdrawal symptoms. It generally has been believed that under medical supervision, an extended taper to withdraw from methadone will prevent discomfort. This "conventional wisdom" must be tempered by a recent finding (60) that "the development of an organic mood syndrome is a common occurrence in patients undergoing slow detoxification from methadone maintenance and is associated with a poor outcome." Whether this effect is specific to methadone withdrawal or applies generally to opiate withdrawal could not be answered by the study.

In addition, the apparent long-term opiate abstinence syndrome is still poorly understood. The prevalence of continuing or recurring opiate "craving" or "hunger," even after successful physiological withdrawal from opiates, is a compelling rationale for being conservative about planned withdrawal from methadone treatment, certainly for long-term addicts.

The hard fact is that we do not yet know how to improve post-detoxification outcomes for methadone patients. Certainly, addressing the relationship between patients' affective states and the protracted withdrawal syndrome (61) is a line of investigation worth pursuing. Research should also be conducted on methods to reduce the stigma and regulatory demands associated with methadone maintenance therapy. Consideration should be given to expanding methadone medical maintenance (MMM) (62, 63). Until we learn more through careful research, it is unwise to structure methadone programs and their financing so as to discourage or impede long-term maintenance, and at the same time to pressure patients overtly to accept abstinence by heralding its supposed desirability or superiority (64).

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Methadone Advocacy:

The Voice of the Patient

Joycelyn Woods, M.A.

Abstract

This decade will see great strides in the acceptance of methadone treatment for heroin addiction, as a result of clear scientific and clinical evidence of its efficacy, and strong methadone advocacy. The new proposal for rule making (NPRM) will help the medical profession accept methadone treatment as beneficial for opiate addiction and realize that it should be more accessible to patients from trained physicians in the community. This will be the first step in reducing the stigma and prejudice that continue to hinder the availability of this lifesaving medication to all who need it.

Methadone advocacy has grown into a powerful network of groups working toward the same major goals. As the premier methadone advocacy organization and the voice for methadone patients, the National Alliance of Methadone Advocates (NAMA) will promote the view that methadone patients are to be judged by the contributions they make to their families and communities.

Key Words: Methadone advocacy, patient rights, stigma, staff and professional attitudes.

Introduction

STIGMA, PREJUDICE AND DISCRIMINATION have become the greatest barriers to recovery confronting methadone patients today (1 – 3). Securing employment and then maintaining a stable, responsible lifestyle is an important aspect of methadone treatment and recovery. But the employed methadone patients live with the constant fear that they will be discovered. Despite the fact that they are protected by the Americans with Disabilities Act (ADA), these patients risk losing their jobs merely for being enrolled in a methadone program (4). Many of these patients do not challenge their employers because they do not realize that it is against the law to be fired for this reason. Nor do they know how to proceed to challenge such a decision. Employment is not the only area in which methadone patients encounter discrimination. They are also excluded from schools, training opportunities and service programs. Thus the road to recovery for methadone patients is difficult and filled with obstacles (5, 6). From the first day they enter treatment, methadone patients find opposition to their enrollment in the program.

Some of the greatest prejudice methadone patients experience comes from the methadone providers (7 – 9). Studies have found that approximately half of the programs administer subtherapeutic doses which encourage patients to withdraw prematurely (10 – 13). Other studies have found that professionals employed in methadone programs have a profound ambivalence regarding methadone treatment — which is not surprising considering the lack of training in medical and graduate schools (14 – 16). Patients become disillusioned about methadone treatment when they encounter condemnation and ambivalence from program staff.

The attitudes of a majority of methadone treatment patients are also influenced by the media, rather than by the results of scientific

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research (5, 17–19). This is not to imply that there are no good methadone programs. Yet all too ofen, patients find themselves fighting against a system that tolerates methadone maintenance treatment as a necessary evil. Until patients know what quality treatment is and believe that they are worthy of it, the situation will not change (20, 21). The formation of advocacy groups in which patients and enlightened professionals work together will lead to more methadone treatment programs that deliver quality treatment.

The National Alliance of Methadone Advocates

The National Alliance of Methadone Advocates (NAMA) was organized in 1988, when a group of methadone patients and professionals met to discuss the problems confronting patients and programs (22). Initially NAMA was envisioned as a small organization, the primary purpose of which was to change policy and educate the public and policy makers about the benefits of methadone treatment. However, as patients heard about NAMA they began to ask for help with problems that they encountered. Today, NAMA, with 48 affiliated groups in this country, serves as the premier methadone advocacy organization to represent the interests and concerns of patients.

Twelve foreign groups, themselves national organizations, together with those in this country, make up a worldwide network focused on the same basic goals (23). The Bruger Foreningen (Danish Drug Users Union) has established a community that welcomes active drug users and methadone patients in Denmark (J. Kjaer, personal communication). Their president, Joergen Kjaer, represents the interests of drug users on the National Drugs Advisory Board, which is a Danish policymaking council. The British Methadone Alliance (BMA) sponsored their first national methadone conference in April 2000. The BMA has also been outspoken this past year regarding the new proposed methadone licensing in Great Britain (24). Other affiliates include the Australian IV League, Gruppo SIMS (Italy), Bruker Foreningen i Tonsberg (Norway) and New Zealand Methadone Advocates. NAMA publications have been translated into Spanish, French, Danish and Italian. The total membership of NAMA, including the affiliates and chapters, is estimated to be about 15,000 individuals from fourteen countries (J. DePasquale, personal communication).

In the United States, those states with large patient populations have their own chapter of NAMA (25). Some of the NAMA chapters work within specific methadone programs, or at the local, state or regional level, to end the prejudice against methadone patients and protect their civil rights. These groups do not receive any funding and depend on the dedication of a few patients who have made a commitment to methadone advocacy.

A Change Is Due:
New Rules and New Prospects

On July 22, 1999, the Center for Substance Abuse Treatment (CSAT) and the Substance Abuse and Mental Health Services Administration (SAMHSA) announced a new proposal for rule making (NPRM) in the Federal Register (26). Under this proposed new system, the federal regulations would be repealed and methadone treatment would no longer be regulated by the Food and Drug Administration. Oversight would be handed over to CSAT and methadone treatment, like all other areas of medicine, would be based on an accreditation system.

The intent of the NPRM is to transform methadone treatment, from a highly regulated procedure that physicians avoid, into a normal medical procedure. This will be the first important step toward incorporating methadone treatment into the practice of medicine (27).

The NPRM contains important changes for methadone patients. The accreditation system includes patient satisfaction surveys and encourages the participation of patients in clinic policy (26, 28). Perhaps the most attractive change for patients will include a more progressive take- home schedule. The NPRM uses guidelines that are similar to the current Federal Code to determine if a patient is sufficiently responsible to receive a prescription for take-home medication. These guidelines also liberalize the allowable amount of take-home medication. Under the current federal guidelines, a patient cannot receive more than a one-week supply of medication, with one dose to be administered at the clinic. The NPRM, however, extends take-home medication to thirty days, with one dose administered at the clinic. This is intended to facilitate a more tolerant system, which will allow a patient to undertake goals and projects that were previously impossible, and, thereby, to promote self-esteem. A liberalized take-home policy will also have a major impact on physicians, who cannot now use their training or expertise to make judgments about which patients are responsible with their medication.

However, states and many local areas also regulate methadone treatment. Their rules are generally more rigid than the federal guidelines (28). At the present time, most of the states are reviewing their regulations. While some states may decide that they are responsible for regulation and become even more restrictive in regulating methadone, it appears that most are beginning to rethink their role. In order for methadone treatment to be accepted as a valid medical procedure, it is imperative that methadone treatment be prescribed by trained physicians in office-based practice (16, 27).

NAMA's Grievance Report Project

The announcement of the NPRM encouraged NAMA to develop a grievance-reporting system that would give patients the opportunity to register complaints against providers, state agencies, support services, criminal justice agencies, health-care providers, employers, vocational agencies, and others. These grievances would be investigated by methadone advocates rather than by agencies, which can be difficult to access. Most complainants need information and direction regarding their respective grievances. Under the direction of an NAMA advocate, complainants are informed about their rights and to whom they are to communicate if their rights have been violated (T. Scro, personal communication). At the end of the year, the grievances will be analyzed and reported to the respective agencies. The important aspect of this analysis is that trends will be examined, and first-hand knowledge will become available regarding practices in specific programs or states.

The primary complaint made to NAMA is that patients are not receiving an adequate methadone dose. Numerous studies have reported that the majority of programs do not prescribe an adequate dose (10–12, 29). A related complaint is that patients are not receiving adequate pain medication or, in some cases, any at all.

The second most common complaint concerns the administrative discharge policies of programs which arbitrarily discharge patients without adhering to the recommended medically supervised procedures. Relapse into heroin use, criminal activity to obtain money to purchase heroin, or possible death by overdose are often the consequences.

Pain Medication and Methadone Patients

Methadone patients who need pain medication for medical reasons are at high risk for receiving inadequate relief of pain (30). There are a number of reasons for this. Many health professionals believe that methadone patients will obtain analgesia from the methadone, or they fail to realize the potential for tolerance in methadone-maintained patients. Also, the personal attitudes of the medical staff about illicit drug use may overwhelm the need to provide adequate pain relief. Patients' complaints are perceived as manipulations to receive opioids for other than pain relief. Some clinicians may believe that they are protecting the patient when they do not prescribe adequate pain medication. Unfortunately, the opposite is true, as inadequate pain medication, particularly in patients with a history of drug use, actually places many patients at risk of relapse should they attempt to find relief from pain through illicit means. The result is that many methadone patients who have needed medication for pain relief did not receive it.

With the high incidence of HIV infection and the increasing prevalence of hepatitis C virus among methadone patients, it is imperative that the medical profession recognize the need for adequate training regarding addiction. When treated humanely and with compassion, opiate-dependent patients should be no more difficult to treat than nondependent patients. The opiate-dependent patient deserves the same quality of care as any other patient.

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THEME ISSUE
GASTROENTEROLOGY AND HEPATOLOGY AT THE MOUNT SINAI HOSPITAL, 1852–2000 — PART 3

Jeremy Hugh Baron and Henry D. Janowitz, guest editors

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Planting Seeds of Knowledge about Inflammatory Bowel Disease:

Half a Century of Science, Prescience, and Prophecy in the Pages of Mount Sinai's Journal

David B. Sachar, M.D.

Abstract

This is a review of those clinical observations, innovative concepts, and predictions concerning inflammatory bowel disease that were first published in *The Journal of the Mount Sinai Hospital*, renamed in 1970 *The Mount Sinai Journal of Medicine*. The review was based on a hand search of every volume of *The Journal* from its inception in 1934 to the present day.

Key Words: Crohn's disease, ulcerative colitis, inflammatory bowel disease, The Journal of The Mount Sinai Hospital, The Mount Sinai Journal of Medicine.

THIS IS SURELY THE AGE OF "Evidence-Based Medicine." In the courtrooms of academia, the only "admissible evidence" these days seems to be fully-powered randomized clinical trials. By this restrictive criterion, though, we pay attention only to the final product — the harvested fruit. But what about the seeds? What about the original observations and seminal ideas that bore fruit only after many years of cultivation?

In March of 1997, the distinguished physician and editor, Frank Davidoff, lectured at Medical Grand Rounds at The Mount Sinai Hospital. His talk, entitled "In the teeth of the evidence: The curious case of evidence-based medicine," included the following statement (1): "All good science begins with good observations, but observations serve largely to generate hypotheses rather than confirm them." The speaker clearly intended to emphasize the importance of "confirmation," harvesting the fruit. In this essay, by contrast, I intend to emphasize the "generation," the planting of the seeds.

A pair of "Theme Issues" in this journal last year has already surveyed the many contributions of Mount Sinai doctors to the field of inflammatory bowel disease (IBD). I have, however, set myself a rather different agenda. Specifically, I shall review those "good observations," innovative concepts, and predictions concerning IBD that were first published in *The Journal of the Mount Sinai Hospital*, renamed in 1970 as *The Mount Sinai Journal of Medicine*. This review is based on a hand search of every volume of *The Journal* from its inception in 1934 to the present day.

Anatomic Distribution

Although "regional ileitis" had been thoroughly described in two nearly simultaneous presentations in May 1932 by Crohn, Ginzburg, and Oppenheimer (2, 3), it took more than 20 years before the same pathologic process in the colon was firmly classified as part of the same disease (4). Nonetheless, Ginzburg and Oppenheimer's initial compilation of cases of "non-specific granulomata of the intestine" (2) meticulously described "localized hypertrophic colitis" associated with peri-anal fistula, an observation repeated by Crohn, Garlock, and Yarnis 15 years later and further emphasized in a *Journal of the Mount Sinai Hospital* abstract (5) regarding the entity of "segmental right-sided colitis": "Peri-anal and peri-rectal fistulas are very common."

While it was the team of a British surgeon, H.E. Lockhart-Mummery, and pathologist, Basil Morson, who argued most strongly for classifying granulomatous colitis as an integral part of Crohn's disease (6), this concept received its major impetus in the United States from the work of Mount Sinai radiologists, particularly

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B.S. Wolf and especially R.H. Marshak (7). Indeed, the classic, most exhaustive description of the features and differential diagnosis of ulcerative and granulomatous colitis appeared in a 59-page article in *The Journal of the Mount Sinai Hospital* by Marshak and Lindner in 1966 (8). This radiologic magnum opus was often reproduced and modified by its authors — as in a *Mount Sinai Journal of Medicine* paper (9) that prefigured a chapter in their classic W.B. Saunders textbook, *Radiology of the Colon* — but the clarity and thoroughness of the 1966 publication was never surpassed. Indeed, as Henry Janowitz foretold in his introduction to the 1966 paper (10): "This exhaustive study and detailed illustration of the radiographic features of the major inflammatory disorders of the colon by Drs. Marshak and Lindner will, I believe, contribute enormously to our sorting out of this baffling group of diseases."

A different view of ulcerative and granulomatous colitis, however, from a colonoscopic perspective, was outlined in 1975, in a paper by Jerome Waye (11), comprising "an in-depth review based on a personal experience of several thousand colonoscopies." This whole topic of recognizing Crohn's disease of the colon has also been reviewed in *The Mount Sinai Journal of Medicine* by one of the pioneering investigators of this disorder, Arthur Lindner, a former fellow in gastroenterology at The Mount Sinai Hospital (12).

Meanwhile, as Crohn's disease was being increasingly recognized in the colon, other *Journal of the Mount Sinai Hospital* publications and abstracts throughout the 1950s were calling attention to involvement of the stomach, duodenum, and jejunum (13–15). (It is interesting that the lure of studying IBD at Mount Sinai was so strong that the principal review of Crohn's gastroduodenitis (14) was written by Alexander Richman, chief of the Liver Clinic who was primarily a specialist in hepatic and pancreatic diseases). Further classic descriptions of gastric and duodenal Crohn's disease, accompanied by magnificent radiographs, appeared subsequently in the "Radiologic Notes" section of *The Mount Sinai Journal of Medicine* edited by C. Bloch and H.M. Peck (16, 17).

Natural History and Epidemiology

Throughout the 1960s, even before establishing himself as the pioneer of immunosuppressive therapy for IBD in the United States, Burton Korelitz, then a young gastroenterologist at The Mount Sinai Hospital, was a leading chronicler of the natural history of ulcerative colitis and Crohn's disease. As early as 1962, he had begun to publish, together with a pediatrician, Donald Gribetz, their observations on the course of ulcerative colitis in children. In 1968, *The Journal of the Mount Sinai Hospital* carried Korelitz's seminal paper on the prognosis of granulomatous colitis in childhood (18). By 1979, Korelitz had accumulated experience with more than 350 patients with Crohn's disease. His report in *The Mount Sinai Journal of Medicine* that year (19) was a landmark in establishing the scientific value of clinical experience garnered by scholarly specialists in private practice.

From a broader perspective of global epidemiology, Mount Sinai's chairman of surgery, Arthur Aufses, Jr., made a remarkably accurate prediction at an IBD symposium in 1982 marking 50 years' experience with IBD and celebrating 25 years of Henry Janowitz's directorship of Mount Sinai's Division of Gastroenterology. On that occasion, Dr. Aufses said (20): "If I had to venture a guess, I would say that granulomatous [Crohn's] disease, which has been on a marked increase in the northern parts of the world, will slowly plateau and then begin to decline. That will be followed by increases in its incidence in other parts of the world, where they don't see very much of it now." As usual, Aufses's crystal ball proved reliable.

Complications

Although Mount Sinai physicians in 1987 were most strongly emphasizing the external origins of upper gastrointesinal (GI) fistulas in Crohn's disease (21), *The Journal of the Mount Sinai Hospital*, as early as 1948, carried a paper recognizing duodenal fistula as colonic in origin, and describing its surgical correction by simple closure of the duodenal hole and definitive resection of the diseased colon (22). Similarly, an early paper on "gastrocolic fistula" clearly identified this complication as arising from "transmural colitis" and at one point in its text used the more accurate term, "cologastric fistula" (23). A much rarer complication involving the upper GI tract is pancreatitis supposedly associated with primary Crohn's disease of the duodenum. One of the earliest reports (actually only the third paper) describing this association appeared in *The Mount Sinai Journal of Medicine* in 1987 (24).

Important observations concerning the much more common complication of lower GI tract fistulization were reported by Korelitz in

The Mount Sinai Journal of Medicine in 1984 (25). His review of 22 patients with ileosigmoid and ileorectal fistulae called early attention to two cardinal principles, both insufficiently appreciated even today. The first point was that "the entero-enteric fistula does not require surgical intervention for its own sake," since it was often asymptomatic and even in cases requiring treatment might well respond to medical therapy. The second key concept was his emphasis on identifying "the segment of origin" — in other words, carefully distinguishing the perpetrator (site of origin) from the innocent bystander victim (the site of re-entry).

Another set of Crohn's disease manifestations largely clarified by Mount Sinai investigators comprised urologic complications. Although a number of Mount Sinai papers from the 1960s are often cited as the earliest publications on this topic, the urologic complications of regional ileitis were first described by Ginzburg and Oppenheimer in the *Journal of Urology* in 1948 and abstracted shortly after in *The Journal of the Mount Sinai Hospital* (26). It should be noted that this same Gordon Oppenheimer of "Crohn, Ginzburg, and Oppenheimer" fame was in fact an eminent urologist. In this article, patients were reported as presenting with retroperitoneal abscesses; but their characteristic symptom of lower extremity pain and limp — prominently described in 1969 by Daniel Present et al., one of IBD's most productive investigators (27) — had actually been emphasized some years before in a radiological vignette in *The Journal of the Mount Sinai Hospital* (28). In this brief report, a patient was described with "severe pain in the lumbosacral region radiating to both legs, associated with difficulty in walking." The paper called attention to the complication of presacral abscess presenting as hip pain and being confused with an orthopedic problem. The correct diagnosis was revealed by a plain film of the spine showing air in the presacral space!

Two other rarely recognized associations or complications of IBD that received some of their earliest attention in *The Journal* were the presentation of regional ileitis as gross rectal bleeding (29) and the co-existence of ulcerative colitis with hemophilia A (30). Yet the tradition of "good observations" in *The Journal* is not restricted to papers from long ago. A very recent issue of *The Mount Sinai Journal of Medicine* carried only the second published case report of a preoperative diagnosis of gallstone ileus in Crohn's disease, and the only one without biliary-enteric fistula (31).

Extraintestinal Manifestations

Few Mount Sinai papers on IBD, at least since the landmark *JAMA* article of 1932 on regional ileitis (2), have been cited as frequently in the medical literature as the 1976 review of extraintestinal manifestations in *Medicine* by Greenstein et al. (32). This analysis of 700 cases of IBD distinguished between "colitis-associated" conditions and those attributable to "small bowel pathophysiology." Yet it is noteworthy that this attempt at classification was foreshadowed more than 20 years earlier in the pages of *The Journal of the Mount Sinai Hospital* by Albert Cornell, then chief of the Gastro-Intestinal Clinic of The Mount Sinai Hospital (33). Moreover, one of the early efforts at treating an extraintestinal complication on the basis of a pathophysiologic rationale was described in *The Mount Sinai Journal of Medicine* when Gelernt and Kreel reported on the use of cyproheptadine, a platelet deaggregrator, in the management of pyoderma gangrenosum (34).

Cancer

It is already well known that Burrill Crohn was an author of the first report of colon cancer in ulcerative colitis (35), and that Leon Ginzburg co-authored the first report of small bowel cancer in regional enteritis (36). It is less widely appreciated, however, that half a dozen key observations about the relationships between cancer and IBD were first published in *The Journal*.

1. Pathology. In 1952, the redoutable Mount Sinai pathologist, Sadao Otani, and the legendary Mount Sinai clinician, Isidore Snapper, teamed up to clarify the relationships among adenomatous polyps, inflammatory polyps, and cancer associated with ulcerative colitis (37). A generation later, Mount Sinai's most prolific surgical author on IBD, Adrian Greenstein, spearheaded a study of the clinical and pathologic features distinguishing colitis-associated from sporadic colorectal cancer (38).

2. Small bowel cancer. Although, as we have seen, Ginzburg et al. first reported jejunal carcinoma complicating Crohn's disease in 1956 in the journal, *Surgery* (36), B.S. Wolf in that same year described the radiologic findings in detail in *The Journal of the Mount Sinai Hospital* (39).

3. Cancer in bypassed loops of bowel. The first American report of ileal cancer in a bypassed bowel segment with Crohn's disease appeared in *The Journal of the Mount Sinai Hospital* in 1970 (40). This paper did not speculate heavily on the pathogenesis of such neoplasms, but it stressed two of the most important clinical implications: first, that these cancers were clinically silent ("...the presence of a clinically silent neoplasm in a bypassed or excluded loop of intestine is extremely difficult to diagnose radiologically...."); and second, that bypass surgery, while efficacious in the short term ("...bypass usually leads to quiescence of the inflammatory process..."), could be detrimental in the long term ("[We] emphasize the possible long-term dangers inherent in this type of surgery."). While many subsequent investigators proposed a variety of biological mechanisms for the occurrence of cancer in excluded loops of bowel, my analysis published in *The Mount Sinai Journal of Medicine* in 1983 (41) indicated that the apparently high frequency of this phenomenon was simply a statistical artefact of the confounding factor of disease duration: "...it is not the bypassed loop itself that puts the patient at risk for cancer; it is the long duration of the disease."

4. Left-sided ulcerative colitis. While conventional wisdom had held that only patients with ulcerative pancolitis were at significantly increased risk for colorectal cancer, our 1979 study in *The Mount Sinai Journal of Medicine* pointedly called attention to the risk in less-than- universal colitis (38): "It is important to recognize that after a sufficiently long interval, cancer may develop in left-sided as well as in universal colitis."

5. Mortality. Another prevalent concept dispelled in this same 1979 paper was that the case-fatality rate in colitis-associated colorectal cancer was much higher than in sporadic cancer (38): "The long-term mortality from colitis-associated cancer did not appear to be worse than that from colorectal cancer in the general population."

6. Cancer in Crohn's colitis. Perhaps the most tenacious myth concerning colorectal cancer in IBD has been that the risk is much greater in ulcerative colitis than in Crohn's disease of the colon. Although the final nails were not driven into the coffin of this widespread misconception until 1994 (42, 43), the strongest prediction of the actuality had appeared in *The Mount Sinai Journal of Medicine* as early as 1983 (41): "When cases of ulcerative and Crohn's colitis of similar anatomical extent are followed for similar durations of time, the two diseases may ultimately prove to have similar increases in risk for colorectal cancer." Subsequent studies indicated that the risks were not only similar, but virtually identical (42).

Medical Therapy

The many contributions of Mount Sinai doctors to the medical therapy of IBD have been amply recounted in previous issues of this journal (44–46) and do not need to be repeated here. Yet it is worth noting how often the most seminal therapeutic principles found early and forceful expression in the pages of *The Mount Sinai Journal of Medicine*. Two symposia in particular provided occasion for giants in the field, from both home and abroad, to demonstrate their prescient vision in the area of medical treatment.

First was the celebratory Anniversary Symposium of 1982 already mentioned in the section on Natural History and Epidemiology above. It was ambitiously entitled, "Inflammatory Bowel Disease: The Next Fifty Years," and even then five of the most vital current trends in therapy were foreseen. First, Korelitz predicted the modern movement toward earlier introduction of 6-mercaptopurine (6-MP) in the management of Crohn's disease (47): "Perhaps when we feel more comfortable with its use it might be justified even earlier in the course, when the disease is still considered mild." In the same presentation, he also accurately foretold two more guiding principles in present-day immunosuppressive treatment: its indefinite continuation for long-term maintenance of remission, and its efficacy in ulcerative colitis as well as in Crohn's disease: "The results have been impressive and suggest that the response rate in ulcerative colitis is similar to that in Crohn's disease.... There is no longer justification for the belief that predisposition to carcinoma in long-standing ulcerative colitis warrants postponing double blind trials of 6-MP similar to those conducted in Crohn's disease."

A fourth "new wave" of therapy was predicted by both Henry Janowitz and John Lennard-Jones at that symposium nearly 20 years ago, namely, the ascendancy of antibiotics in the treatment of Crohn's disease (48, 49). Lennard-Jones — to this day still unsurpassed in his genius as a clinical investigator in IBD — foresaw the 21st century's emphasis on designing biological agents to target specific points in the pathogenetic pathway of the diseases (48): "I think we'll find out how the treatments affect...pathogenetic mechanisms.... I suspect that our medical treatment is going to improve because we are going to be able to design the treatment to affect those pathogenetic mechanisms." This statement was made fully 15 years before the introduction of infliximab and related revolutionary anti-cytokine therapies!

In fact, in his 1983 remarks, Lennard-Jones's prescience extended beyond the boundaries of medical treatment into accurate visions of modern pathogenetic research: "We'll take a particular interest in the bacterial flora of the gut and its relationship with the genetic immunological status of the host." Fifteen years later, a mountain of experimental evidence has borne out his prediction. Similarly, "We'll learn a lot about chemical transmitters in the gut wall." Today's pharmaceutical research on IBD is, of course, focused almost entirely on these chemical transmitters. On this same occasion, Lennard-Jones made yet another bold prediction regarding etiology and epidemiology: "I think we'll also find that there is an environmental factor which accounts for differences in epidemiological incidence in various countries." I find this concept highly attractive, but so far insufficient evidence has been accumulated to permit submission to any jury, grand or otherwise.

A second, more recent Mount Sinai forum for "science, prescience, and prediction" regarding IBD took place in December 1989, at a Symposium entitled, "Inflammatory Bowel Disease Therapies for the 1990s: Scientific Basis and Clinical Experience" (50). Here again, the published proceedings in *The Mount Sinai Journal of Medicine* provided glimpses into at least three more innovative therapeutic avenues that would eventually culminate in clinical trial "evidence" in subsequent years. First, the indefatigable pioneer of cyclosporine treatment for ulcerative colitis, Simon Lichtiger, presented the first reports of the effectiveness of this agent both for severe steroid-resistant ulcerative colitis and for fistulizing Crohn's disease (51).

Second, Korelitz advanced the concept of pushing progressively higher doses of 6-MP, when required, to achieve therapeutic benefit (52): "There does seem to be correlation with dosing and effectiveness, because if we start at one dose and it isn't successful, very often I see that when the dose is raised, within a brief time something begins to happen.... If the patient's white cell count has not fallen and we haven't achieved therapeutic effectiveness, I will push for a bigger dose." If they had had to wait for the "admissible evidence" demanded by current academic fashion, countless patients would have been denied the benefits of this incontrovertibly correct approach.

And finally, Henry Janowitz, the father of academic gastroenterology at Mount Sinai, accurately predicted both the modest effectiveness of 5-aminosalicylates (5-ASA) and the greater effectiveness of immunosuppressives in the prevention of relapse of Crohn's disease (53): "I think that 5-ASA will offer a modest degree of protection against relapse in maintenance studies in Crohn's disease as it does in ulcerative colitis when studied against placebo. We now look forward to the continuing follow-up of the immunosuppressive agents in these diseases."

Surgery

As with medical therapy, surgery for IBD has been greatly advanced by the staff of The Mount Sinai Hospital (54). While most of these contributions have of course been published in the wider medical and surgical literature, *The Mount Sinai Journal of Medicine* has recorded its share of seminal observations. For example, an early report of the use of a rectal mucosal advancement flap for rectovaginal fistula appeared in a 1983 issue (55). With even broader impact, *The Mount Sinai Journal of Medicine* in that same year reported Irwin Gelernt's unrivaled early experience in the United States with 300 patients receiving a continent ileostomy (Kock pouch) for ulcerative colitis (56).

Looking even farther into the future, however, John Lennard-Jones, speaking at Mount Sinai, predicted the eclipse of the continent ileostomy by newer sphincter-sparing procedures on the horizon (57): "I don't think that continent ileostomy is the full answer. I think that the full answer is going to leave anatomy much more as it is, that is to say with the use of the anus. Then I think surgery will be more acceptable and I think we as physicians will be recommending it more frequently and our patients will be accepting it more readily." Speaking at the same venue, the distinguished British surgeon, John Alexander-Williams, agreed with this assessment and also provided his audience and *The Journal*'s readership with an early overview of the newly-emerging intestine-sparing procedure of strictureplasty (57).

Of course, predating all the continent variations on the technique was the standard Brooke ileostomy, a procedure extensively studied and perfected by a senior Mount Sinai surgeon, Albert S. Lyons. The founder of patient-oriented ileostomy associations in the United States, Lyons focused on the central importance of patients' psychosocial adjustment to ileostomy, in a 1983 article in *The Mount Sinai Journal of Medicine* (58), only shortly after Mount Sinai's first paper on the subject (59) and long before surgical "quality of life" studies in IBD had become academically fashionable. More recently, *The Mount Sinai Journal of Medicine* again provided the forum for a ground-breaking study bringing quantitative science to bear on such elusive but critical issues as individual coping mechanisms and family dynamics in the course of IBD (60).

Postoperative Recurrence of Crohn's Disease

It has often been said that the inexorable tendency of Crohn's disease to recur following surgical resection is still the thorniest single problem in present-day management of inflammatory bowel disease (61). The medical and surgical literature of the past 20 years is replete with studies of this phenomenon, its natural history, and attempts at its prevention. But as early as the 1950s, papers in *The Journal of the Mount Sinai Hospital* were already focusing this troublesome issue. An interdisciplinary conference of ten Mount Sinai clinicians in January 1952 devoted the great bulk of its attention to detailed discussions by Burrill Crohn and the surgeon, Ralph Colp, concerning cases of postoperative recurrence of ileitis and ileocolitis (62). In this context, it is noteworthy that even at this early date, Mount Sinai surgeons and gastroenterologists were prefiguring the surgical conservatism of today; in Colp's words, "In the present state of our knowledge, we are operating on these patients only when our hand is forced by intestinal obstruction, fistulae, and abscess formation."

Fully forty-five years ago, in a *Journal of the Mount Sinai Hospital* Symposium edited by Dr. Crohn, Henry Janowitz provided an overview of "Problems of Regional Enteritis" that has scarcely been improved upon to the present day (63). His review included several pathophysiologic insights (e.g., the suggestion that "the noxious agent is present in the intestinal stream") that are currently being validated (64). With particular regard to the problem of postoperative recurrence, Dr. Janowitz drew both pathophysiologic and therapeutic conclusions: regarding the former, "The hypothesis of widespread initial lesions...might explain the high incidence of recurrence following operation even though biopsy at the site of resection or by-pass may be entirely negative"; and regarding the latter, "With the increasing recognition that the rate of recurrence is a function of the length of follow-up, and with increasing numbers of recurrences, the [surgical] approach to therapy is now in a disillusioned phase." It must be noted that what Janowitz so confidently alluded to in *The Journal of the Mount Sinai Hospital* as "increasing recognition" in 1955 was validated by "admissible evidence" in the *New England Journal of Medicine* only 20 years later (65)!

History

This essay was not undertaken to replicate last year's historical review of Mount Sinai's contributions to the study of IBD (66), but it has instead tried to assess the unique role of *The Mount Sinai Journal* over the last half century as a seedbed and sounding board for innovative and forward-looking thoughts about the nature and management of these disorders. Yet this assessment would not be complete without some mention of several remarkable historical reviews that have appeared in these pages in years past, especially since these historical perspectives have looked not only backward but also forward.

Before the current set of three theme issues edited by Jeremy Hugh Baron and Henry D. Janowitz, there were at least seven other historical surveys published in this journal between 1945 and 1993 that deserve citation:

1. 1945. In a retrospective of "Gastroenterology at The Mount Sinai Hospital" prepared for the Moschowitz Anniversary Issue of *The Journal of the Mount Sinai Hospital* (67), Burrill Crohn was especially gracious in his discussion of the disease that ultimately came to bear his name:

> ...in 1932, dated from The Mount Sinai Hospital, appeared the first paper or papers [note the plural!] on a new clinical entity "regional ileitis." The earlier pathological and clinical studies on intestinal granulomata had been laid down by Drs. Eli Moschowitz [whom this issue of *The Journal* was honoring] and A.O. Wilensky as early as 1923. The pathological studies of these granulomata had been re-begun by Drs. Leon Ginzberg [*sic*] and Gordon Oppenheimer. The combination of these studies with the clinical and surgical observa-

> tions of myself and Dr. A.A. Berg led in 1932 to the formulation of the entity of "ileitis." With practically no hesitation, with little scientific criticism, but with many constructive additions, the medical profession has accepted ileitis, or regional enteritis, as an established clinical concept.... The Attending Staff of this hospital have thus been given proper credit for the recognition of a disease, which knows no limited geographical incidence and which provides an ample and new arena for extensive surgical operative skill and original initiative.

2. 1951. In the Albert A. Berg Memorial Issue of *The Journal of the Mount Sinai Hospital*, Crohn once again downplayed his own role and lavished primary credit upon Dr. Berg, Mount Sinai's late chief of surgery, for developing the concepts of regional ileitis and "right-sided or segmental ulcerative colitis," as well as for advancing the "increasing utility of ileostomy for severe ulcerative colitis and the feasibility of subsequent total colectomy for otherwise incurable forms of universal colitis...." (68).

3. 1955. Under the editorship of Dr. Lester R. Tuchman, *The Journal of the Mount Sinai Hospital* in 1955 published the first in a series of symposia to "cover areas in which workers at The Mount Sinai Hospital are at the present time engaged on a broad front, or fields to which they have made significant contributions." The topic was "Regional Ileitis." In an even-handed bow to two men who were both colleagues and rivals, Dr. Tuchman concluded his editorial introduction (69): "Since the seminal paper on Regional Ileitis was by Drs. Crohn, Ginzburg and Oppenheimer, it is fitting that the first be Guest Editor and the second the author of the article on its surgical management." In his "Reminiscences," Crohn paid tribute yet again to the contributions of Berg, Ginzburg, and Oppenheimer to the recognition of regional ileitis as a clinical and pathologic entity (70). Remarkably, both in the closing paragraphs of this article, as well as in a 1949 paper (13), Crohn prefigured a designation of inflammatory bowel diseases that has only very recently taken shape as the "Rome" (71) and "Vienna" (72) Classifications of Crohn's disease!

4. 1966. The first section of this paper, "Anatomic Distribution," opened with a review of *The Journal*'s contributions to an understanding of involvement of the colon by Crohn's disease. For those interested in a more detailed review of the evolution of the history of this concept, an historical gem is nestled in the pages of a 1966 issue of *The Journal of the Mount Sinai Hospital* (73). Entitled, "Granulomatous colitis: An attempt at clarification," and authored by Crohn and Yarnis, this article provides a fascinating, step-by-step chronicle of what Lindner (12) much later referred to as "Recognizing Crohn's disease of the colon." In their historical retrospective, Crohn and Yarnis credit British workers of the 1950s for first recognizing the connections between "segmental" or "right-sided" colitis and the granulomatous disease, regional ileitis. They go on to acknowledge frankly, "Many of us, myself [presumably Crohn] in particular, altered opinion slowly, hesitating to admit that the segmental [cases of colitis] were truly granulomatous in nature. But over the course of years and with more extensive study on the part of the pathologist, it would seem that not only because of fact, but also in the interest of simplification one must accept as truly granulomatous disease all cases of so-called right-sided colitis." These two giants in the field of IBD also called attention to the phenomenon we now call "rectal sparing," and they confessed ignorance concerning its cause: "The most interesting fact here is that even when observed for years, this process [of granulomatous disease involving the entire colon] will not pass the rectosigmoid. It would almost appear that the rectosigmoid area constitutes a barrier to the progression of the pathological process *provided no surgery is performed* [italics added to emphasize yet another of their seminal observations!]. Why the lesion halts at this nodal point is difficult to understand." Thirty-five years later, we are none the wiser on this question.

5. 1973. In a memoir written for *The Mount Sinai Journal of Medicine* (74), Leon Ginzburg pulled off an extraordinary feat. He published a four-page article chronicling the history of regional enteritis without once mentioning the name of Burrill Crohn — except in a dismissive six-word footnote in very small type, appended to his description of the twelve cases that he and Oppenheimer had so laboriously collected and meticulously studied: "*Dr. Crohn later added two more." The insertion of this footnote seems reminiscent of the practice of bequeathing one dollar to a particularly unfavored relative, just to prove the point that the disinheritance was not the result of an innocent oversight. By the time of a subsequent memoir ten years later (75), Ginzburg's rhetoric may have softened somewhat, but not his heart, in the judgment of those of us privy to his uninhibited correspondence and conversations.

6. 1983. In a more objective vein, Dr. Janowitz provided an overview of "The road to Crohn's disease" that emphasized three cardinal points (76): (a) that the disease was relatively new in appearance and increasing in incidence; (b) that it affected the entire GI tract as well as "overflowing" into surrounding tissues; and (c) that it had systemic effects ("an impact on the organism") beyond the gastrointestinal tract and its immediately adjacent organs.

7. 1993. At the dedication of the Dr. Henry D. Janowitz Division of Gastroenterology at Mount Sinai on December 8, 1992, Dr. Daniel Present delivered a review of "Advances in knowledge of inflammatory bowel disease at Mount Sinai Medical Center" (77). In so doing, he paid homage to our teacher and mentor, Dr. Janowitz; modestly understated his own many contributions; and paid tribute to all those who have played, are playing, and will play important roles in the continuing study, elucidation, and amelioration of these cruel and baffling diseases.

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Hepatology at Mount Sinai:

The Present and the Future

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Abstract

The Division of Liver Disease at Mount Sinai, now into its fifth decade, has evolved through two remarkable periods in its development and is on the cusp of a third exciting era. The first, extending from the division's creation in 1957 to the retirement in 1988 of its first division chief, Fenton Schaffner, was characterized by brilliant clinical and pathophysiologic insights derived from the unique collaboration of Schaffner, a master clinician, with Hans Popper, a world renowned pathologist widely acknowledged as the father of the modern discipline of hepatology. The second, extending from the appointment in 1988 of Paul D. Berk as Schaffner's successor to the present day, has witnessed enormous growth in the clinical and scientific activities of the division, together with the emergence of a world-class liver transplant program at Mount Sinai. During this recent period, an extensive program of formal clinical research was established; the basic research program then expanded into the areas of hepatic transport, molecular virology, and the cellular and molecular pathogenesis of hepatic fibrosis; and both the clinical and research productivity of the division increased dramatically. A major undertaking, now in its second year, has been the creation of the Center for the Study of Primary Biliary Cirrhosis; Mount Sinai has contributed important advances toward the understanding of this disease. Funding for the Center, from the Artzt Family Foundation Trust, supports a series of interrelated basic studies on the immunology and pathobiology of the disease, as well as creation of a unique clinical database, a serum and tissue bank, and a program of clinical studies. This integration of basic and clinical research in pursuit of new methods of diagnosis and treatment serves as a model for the division's continued leadership role.

Key Words: Hepatology, history, Mount Sinai, primary biliary cirrhosis, Popper, H., Schaffner, F., hepatitis B, hepatitis C.

Origin

A LONG HISTORY OF CLINICAL EXPERIENCE and outstanding scientific investigation that extends from bench to bedside has made Mount Sinai synonymous throughout the world with the study and treatment of liver disease. The foundations of its reputation in modern hepatology were laid in the thirty years between the creation of the Division of Liver Disease in the late 1950s, with Fenton Schaffner as its first chief, and his retirement in 1988. Some of the division's seminal contributions include: the identification of the clinical and pathophysiologic significance of cholestasis; recognition of the importance of fibrosis as the final pathway leading from different inciting injuries to the common end result of cirrhosis; elucidation of the nature of chronic viral infections of the liver; and delineation of the clinical spectrum and natural history of primary biliary cirrhosis. Fundamental though they were, these landmark contributions were made with little more than sharp bedside observation, a light microscope, and keen human intellect. The use of special stains to enhance the diagnostic power of light microscopy, or — on occasion — the application of transmission electron microscopy, were the principal inroads made at Mount Sinai by high technology during this period. This was a multidepartmental effort, involving hepatologists, surgeons, pathologists, anatomists, and clinical chemists. Few would dispute, however, that the driving force for more than 30 years came from Hans Popper and Fenton Schaffner, friends and colleagues. Schaffner held joint

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professorships in both Medicine and Pathology. In a coincidence of almost poetic symmetry, Dr. Schaffner's death, on January 24, 2000, occurred on the very day that the January 2000 issue of *The Mount Sinai Journal of Medicine*, containing his last published article, "History of Liver Disease at the Mount Sinai Hospital" (1), was distributed, bringing to a close an extraordinary era.

The Post-Schaffner Era

By the time of Dr. Popper's death in 1988, followed shortly thereafter by Dr. Schaffner's retirement as chief of the division, winds of change had already begun to transform Mount Sinai's liver disease program. The first liver transplant at this institution, performed by Dr. Charles Miller (Mount Sinai School of Medicine [MSSM] class of 1978) in September 1988, initiated a massive, clinical enterprise combining the talents and dedications of the Liver Transplant Surgery Team and the Division of Liver Disease. The appointment of Dr. Paul D. Berk, then chief of Hematology, to succeed Dr. Schaffner as Mount Sinai's second chief of Liver Disease initiated a strategy to complement the outstanding clinical research enterprise with a laboratory program exploring basic mechanisms of liver disease.

In 1988 the Division of Liver Disease had two faculty members, two small NIH grants, and clinical revenues of less than $150,000 annually (Figure). Its faculty roster now stands at sixteen, eleven M.D.s, an M.D./Ph.D., and four Ph.D.s, and its annual clinical faculty practice activity has increased more than ten-fold. The division now carries out diverse research projects supported by five grants from the NIH, extensive support from private, nonprofit foundations, and clinical trial funding from the pharmaceutical industry. The research budget has grown steadily since 1988, and is approaching $3 million annually.

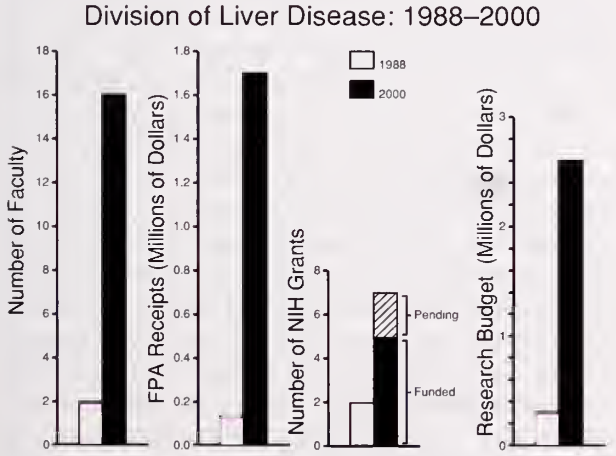

Figure. a. Number of faculty and clinical practice income in 1988 vs 2000. **b.** Number of NIH grants and total research expenditures in 1988 vs 2000.

Clinical Investigation

Over the past 12 years, the Division of Liver Disease has been a model of "translational research." Dr. Henry Bodenheimer, a Schaffner trainee, was recruited from Brown University to become the division's clinical director in 1992. A figure known nationally for his participation in important clinical trials, including those establishing a role for interferon in the treatment of chronic hepatitis C, he has spearheaded the development of a clinical research program that has kept Mount Sinai at the forefront of evolving medical therapies for chronic liver diseases. Most recently, he was named medical director of the Recanati-Miller Transplantation Institute. Dr. Bodenheimer has also played a critical role in the development of training programs in liver disease for both the medical house staff and fellows. This commitment to our training environment was recently highlighted by the awarding of three fellowships from the American Association of the Study of Liver Disease (AASLD)/Schering Advanced Hepatology to divisional trainees, the most of any institution in the country. In addition, Dr. Efsevia Albanis, a 1994 MSSM graduate and currently Senior Research Fellow in the laboratory of Dr. Scott Friedman, won the highly prestigious AASLD/AMGEN Physician Development Award.

In addition to Drs. Bodenheimer and Berk, the clinical staff of the division currently includes Drs. Nancy Bach, Scott Friedman, David Jaffe, Leona Kim-Schluger, Albert Min, Thomas Schiano, Michael Schilsky, and Samuel Sigal. All of them participate in a cooperative enterprise that combines the care of a large and challenging population of patients with liver disease, along with close collaboration with investigators in other departments, such as Drs. Swan Thung and Isabel Fiel from Pathology and Drs. Charles Miller, Myron Schwartz, Patricia Sheiner, Sucru Emre, and other members of the liver transplant surgical team. A selection of recent publications from this clinical program is included in the reference list of this article (2–17).

The investigative interests of the Liver Disease faculty reflect the breadth of Mount Sinai's patient population and the diverse venues in which these patients are seen, including the Faculty Practice suite, The Mount Sinai Hospital Liver Clinic, clinics associated with the liver transplant program, and a satellite office in New Jersey. Shared clinical research interests include: the diagnosis and management of chronic hepatitis, especially that resulting from infection with the hepatitis B and C viruses (2–4); other complications of these infections, including the development of hepatocellular carcinoma (5) and B-cell lymphomas (6); and the utility of various diagnostic studies used in screening for specific complications of liver disease (7). At the same time, faculty members have evolved their own areas of special expertise, on which they have focused both their patient care activities and their clinical investigative programs. Thus, Dr. Albert Min has a strong interest in hepatocellular carcinoma in the setting of chronic liver disease (5). In addition, Dr. Min is currently involved in various Phase II and III clinical trials of novel therapies for hepatitis B and C. Along with Dr. Henry Bodenheimer, he is involved in assessing the efficacy of long-acting interferon in combination with ribavirin for chronic hepatitis C, both in previously untreated patients and in those unresponsive to prior antiviral therapy. With his interest in pretransplant evaluation of patients with end-stage liver disease in the setting of a severe scarcity of donor livers, he has attempted, along with Dr. Thomas Schiano, to find additional prognostic factors for identifying the most suitable pretransplant candidates (7). He is currently analyzing the long-term outcomes of patients transplanted at Mount Sinai for various forms of chronic viral hepatitis.

Dr. Nancy Bach, another Schaffner trainee, supervises a productive office-based program focused on clinical investigation in primary biliary cirrhosis (8). Dr. Bach is also involved in a study assessing the efficacy of combination antiviral treatment in patients with chronic hepatitis C and normal liver enzymes.

Although all the physicians in the division are actively involved in the evaluation and preoperative care of liver transplant candidates, Drs. Leona Kim-Schluger and Thomas Schiano have primary responsibility for postoperative care of transplanted patients, and for identifying specific medical complications that arise in the post-transplant setting (9–11). Dr. Kim-Schluger is also participating in clinical trials of new immunosuppressive agents in liver transplant patients, and is spearheading a pilot study of the long-term efficacy of liver or kidney transplantation in patients infected with human immunodeficiency virus. Dr. Schiano has a particular clinical interest in the treatment of recurrent viral hepatitis after liver transplantation. In this regard, he is involved in studies of passive immunoprophylaxis to prevent recurrent disease in patients undergoing transplant for hepatitis C-related, end-stage liver disease. Having been trained in clinical nutrition, he is also exploring the association between nutrition and the health of the liver, and in the use of herbal and complementary medications for the treatment of liver disease.

Dr. David Jaffe, an outstanding biliary endoscopist, has become a regionally recognized authority on biliary tract disease. His interests include assessing the outcome of patients transplanted for primary sclerosing cholangitis, and screening these patients for possible development of cholangiocarcinoma. Dr. Samuel Sigal's long-standing interest in hepatic regeneration (12) translates into a clinical focus on managing complications of end-stage cirrhosis, such as ascites, electrolyte disturbances, hepatorenal syndrome, portal hypertension, and hepatic encephalopathy. Dr. Sigal's particular interests include managing and evaluating patients who have undergone transjugular intrahepatic portosystemic shunts (TIPS), and caring for patients with hepatocellular carcinoma, especially those who are candidates for percutaneous ethanol injection therapy (PEIT). Dr. Michael Schilsky, recruited from the Albert Einstein College of Medicine in 1999, is a recognized expert on disorders of metal metabolism, including hereditary hemochromatosis and Wilson's disease (13–17). Dr. Schilsky is currently participating in an FDA-sponsored pharmacologic trial with Dr. George Brewer of the University of Michigan, to determine the best initial therapy for the treatment of patients with Wilson's disease and neurologic symptoms. This study is being conducted in Mount Sinai's General Clinical Research Center in collaboration with the Department of Neurology. Dr. Schilsky is also a co-investigator in the National Hemochromatosis Transplant Registry, which is designed to determine the outcome of patients with hemochromatosis who undergo liver transplant. Along with staff from the surgical intensive care unit (SICU) and colleagues from the Transplant Institute, he is initiating a trial of an extracorporeal liver assistance device (ELAD) for patients with fulminant hepatic failure. Depending on the clinical situation, this device will be used either to provide a bridge to liver transplant or to support the patient during recovery of the native liver. Dr. Berk, an authority on jaundice and the hereditary hyperbilirubinemias (18), also has clinical and research interests in primary biliary cirrhosis, hemochromatosis, the porphyrias, and hepatitis C. Thus, the division has broadened both its clinical expertise and clinical research interests over the past twelve years. It is moving toward a goal of having virtually every patient participate in one of its multifaceted clinical research programs.

Bench Research

The last dozen years have witnessed an explosive growth in the discipline of hepatology, as measured by a tripling of attendance at major national and international meetings devoted to the liver, an increase in the number of books and journals devoted to the specialty, and increased emphasis on training in liver disease within the framework of fellowship programs in gastroenterology. The enormous growth in this field is largely a consequence of two major phenomena: the dramatic increase in liver transplantation and the worldwide epidemic of hepatitis C. What is sometimes overlooked is the equally dramatic growth in the application of such basic disciplines as cellular and molecular biology to the study of liver disease, and the increased basic science content of the entire field, as is clearly reflected both at its meetings and within its published literature. The prominence of basic science within the discipline of hepatology, both nationally and internationally, is reflected in parallel changes within the Division of Liver Disease at Mount Sinai. The division currently conducts four major basic science efforts.

Fatty Acid Transport

When the Berk laboratory moved from Hematology to Liver Disease in 1998, it brought with it a well-established program in hepatic metabolism and hepatic transport. While the focus had for many years been on bilirubin (18), the laboratory's interests were evolving, and by 1988 at least half of the effort was focused on the plasma membrane transport of long chain free fatty acids (LCFFA). LCFFAs are increasingly recognized as important intracellular modulators of gene expression, suggesting that control of their intracellular concentrations through regulation of their cellular uptake and efflux would be of great value. However, cellular uptake of LCFFA was long considered an entirely passive, and therefore unregulated, process of relatively little intrinsic interest. Over the past 15 years, studies in the Berk laboratory, which have included research assistant professors Drs. Michael Bradbury and Shengli Zhou, as well as Dr. Xinqing Fan; Decherd Stump, and Chih-Li Kiang, have established that LCFFA uptake under physiologic conditions is mainly a facilitated transport process (19). The laboratory also identified the first putative LCFFA transporter, initially designated "plasma membrane fatty acid binding protein" (FABPpm). Tissue-specific regulation of the expression of this protein and of facilitated LCFFA transport occurs in several cellular and animal models of human disease. In particular, LCFFA uptake is selectively up-regulated in adipocytes, but not in other critical tissues such as liver and cardiac muscle, in a variety of rodent models of obesity and non-insulin-dependent diabetes mellitus (20, 21). The net effect of this change is to divert LCFFA from skeletal and cardiac muscle, where they would be consumed for energy production, into adipose tissue, where they are stored as fat. Thus, the observed changes in LCFFA disposition contribute to perpetuation of the obese phenotype. Conversely, ethanol was found to up-regulate LCFFA uptake selectively in hepatocytes, contributing to alcohol-induced fatty liver (22). Somewhat surprisingly, FABPpm proved to be identical to mitochondrial aspartate aminotransferase (mAspAT) (reviewed in reference 19). Molecular modeling studies of mAspAT, carried out in collaboration with Dr. Frank Guarnieri of the Department of Physiology and Biophysics, have identified a previously unrecognized hydrophobic cleft of suitable size to be an LCFFA-binding site. His laboratory has shown that the plasma membrane and mitochondrial components of mAspAT are both derived from a single message; sorting of the protein to different sub-cellular sites does not involve alternative splicing of the mRNA (23). Ongoing cell biologic studies are elucidating the complex route by which mAspAT traffics to the plasma membrane and is exported from the cell.

Studies of the Hepatitis C Virus

The hepatitis C virus (HCV), now recognized as the principal causative agent of non-A, non-B hepatitis, was first discovered in 1989. Its ~9 kb RNA genome encodes a single polyprotein that is subsequently cleaved by both host and virally encoded enzymes to the various recognized structural and nonstructural proteins characteristic of HCV. Of approximately 4 million Americans who have antibody evidence of having been infected with HCV, only some 15% appear to clear the virus spontaneously. The remainder experience chronic hepatitis of variable severity that persists for decades. Approximately 20% eventually develop cirrhosis and, ultimately, the complications of end-stage liver disease. Chronic HCV infection is now the most frequent indication for liver transplantation in the United States and Western Europe.

The biology of the virus remains poorly understood. Because of the division's growing clinical involvement with hepatitis C, Dr. Andrea Branch, an outstanding authority on plant viroids and on the delta agent (hepatitis D virus, HDV), was recruited from Rockefeller University in 1994 to develop a program of basic studies of the HCV virus. Her highly reasoned critical reviews of what is known about hepatitis C (e.g., reference 24), and of the potential strengths and weaknesses of conventional approaches to both antisense therapy (25–28) and gene therapy (29, 30), have very quickly established her as an important and creative contributor to the field. Recognizing that viral genomes often have overlapping genes, Dr. Branch and her associates, in particular Dr. Jose Walewski and Decherd Stump, developed software that has facilitated their comparative sequence analyses of published HCV isolates, in an effort to identify overlapping, dual-use regions. Their strategy for identifying such regions is based on the degeneracy of the genetic code. Thus, the code for a number of amino acids is fully specified by the first two bases of a codon. Since the third base in this situation is of no consequence for defining the encoded amino acid, it would be anticipated that, over time, random mutations would have resulted in the given amino acid being encoded by any of four sequences, with the same bases in positions 1 and 2, and A, T, G or C in position 3. This variability in position 3 would have no effect on the amino acid sequence of the encoded polypeptide. However, if there were an overlapping reading frame, an insignificant change in base position 3 in one reading frame could produce a significant alteration in the amino acid composition of a polypeptide encoded in an overlapping, alternative reading frame. Based on these theoretical considerations, diverse HCV sequences were obtained from GenBank (Bethesda, MD), and aligned. The proximal portion of the main open reading frame (ORF) was found to contain a region of highly constrained sequence, in which the third base in numerous codons was far more restricted than would be anticipated by chance. When read in the alternative 1+ reading frame, nearly 90% of the retrieved sequences contained at least 124 codons without a stop codon, representing a candidate second or alternate ORF. By contrast, within the same region of HCV RNA, the 2+ reading frame was riddled with stop codons. To determine if this alternate ORF (A-ORF) was biologically significant, two peptides, representing different regions of the encoded A-ORF polypeptide, were synthesized and used to develop assays to detect antibodies against the A-ORF protein. Analysis of sera from patients with chronic HCV demonstrated that an appreciable proportion of them contained antibodies to the A-ORF protein (31), indicating that the protein must be synthesized during chronic HCV infection. Efforts are now ongoing to identify the protein itself in liver samples from infected patients. The identified protein may be of value in improved HCV diagnostics. Moreover, the new protein, as well as the uniquely conserved region of the HCV genome that encodes it, are potential targets for a variety of new anti-HCV therapeutic strategies. It is likely that therapies developed on the basis of these observations will eventually undergo clinical evaluation within our program at Mount Sinai.

Mechanisms, Diagnosis and Treatment of Hepatic Fibrosis

Dr. Scott Friedman, a graduate of the MSSM (class of 1979), returned as a faculty member and director of research in the Division of Liver Disease in November 1997. His return followed an absence of 18 years, which included 15 years at the University of California San Francisco (UCSF), first as a gastroenterology fellow and then as a faculty member. During his tenure at UCSF, he did pioneering research into the underlying causes of scarring, or fibrosis, associated with chronic liver disease. Dr. Friedman was the first to isolate and characterize the hepatic stellate cell, which is the key cell type responsible for scar production in liver (32). This work has led to major insights into how the liver responds to injury, and points the way toward new treatments.

Dr. Friedman's interest in liver disease can be traced directly to Mount Sinai's founding fathers of hepatology, Drs. Schaffner and Popper, whose lectures planted the seeds of interest that led to his specialty. Remarkably, his experimental studies have followed directly from earlier observations by Drs. Popper and Schaffner, who emphasized the stellate cell's potential importance in liver disease. From this initial finding, Dr. Friedman's research has expanded into a comprehensive program exploring the cellular and molecular basis of liver fibrosis, which has spawned parallel efforts in dozens of laboratories and pharmaceutical companies throughout the world (33–38). Liver fibrosis, leading ultimately to cirrhosis, is a serious consequence of excessive alcohol consumption (39), and has assumed major importance as a potential treatment target for the millions of patients infected with hepatitis C (40). In addition to continuing an in-depth exploration of molecular mechanisms of hepatic fibrosis, he is collaborating with Dr. Frank Eng and several other colleagues, in the clinical realm, with the testing of novel diagnostic agents and therapies for hepatic fibrosis. Much of the current excitement about the potential benefits of anti-fibrotic therapy in these important liver diseases can be traced to Dr. Friedman's contributions.

The Pathobiology of Primary Biliary Cirrhosis

Mount Sinai has had a major and productive interest in primary biliary cirrhosis (PBC) for nearly 50 years, with important studies by Drs. Popper and Schaffner illuminating its clinical spectrum, natural history, and histopathologic evolution, as well as the nature and significance of cholestasis. This interest led to the accumulation of a large group of PBC patients, who have participated in numerous trials of medical therapies, and have provided many candidates for Mount Sinai's liver transplant program. Mount Sinai is currently following as many as 600 patients with this uncommon disease, including more than 100 who have received liver transplants and a similar number with advanced disease, who are currently being followed in the pretransplant clinic. The remainder, at earlier stages in their disease, are being followed in either the Liver Disease Associates FPA suite or the Liver Clinic.

As a result of this unique experience, the Artzt Family Foundation Trust recently provided the division with a three-year grant to initiate the Center for the Study of Primary Biliary Cirrhosis at Mount Sinai. The Center will support both clinical and basic science initiatives related to PBC. A major component of the clinical program is the development of a unique patient database, which will eventually contain patient data not only from Mount Sinai, but also from collaborating centers around the world. The database, under development with the assistance of Computer Associates (Islandia, NY), will incorporate *neugents*, a unique artificial intelligence tool capable of identifying previously unrecognized trends and correlations in very large data sets and using them for the formulation of new hypotheses. This database will also support future clinical trials, some of which, we anticipate, will be designed to test hypotheses developed with the *neugents* technology. A serum and tissue bank, linked to the database, will be an important resource for laboratory investigations. The Center is already supporting basic studies in several laboratories, including those of Drs. Berk, Branch, Friedman and Thung. For the most part, these studies represent an extension of ongoing work, such as studies of mitochondrial protein trafficking and hepatic fibrosis, as well as relevant aspects of PBC. A critical component of the program, however, is the creation of a new laboratory devoted specifically to the immunology of PBC. Dr. Joseph Odin, an alumnus of Mount Sinai's M.D./Ph.D. program, has been recruited back to his alma mater from the Johns Hopkins School of Medicine to create this new program. Dr. Odin has had a long interest in the immunology of PBC and most recently has been investigating the role of apoptosis of biliary epithelial cells in the generation of the antimitochondrial antibodies that are characteristic of this disease.

Hepatology in the New Millennium

The Mount Sinai Division of Liver Disease, by virtue of its long tradition and extraordinary recent development, is perfectly positioned to exploit the explosive growth in biomedical research now being witnessed worldwide. This era of science, driven in part by the impending completion of the sequencing of the human genome, is a "golden age of biology," much as the 1940s and 1950s were a golden age for physics, with the harnessing of nuclear energy. Moreover, the trajectory of anticipated divisional growth is aligned perfectly with the institutional commitment to translational research, as articulated in Dean Arthur Rubenstein's Strategic Plan.

What new advances can we expect in the field — at Mount Sinai and elsewhere? New computer technologies, such as the unique patient database described above, will allow investigators to gather and analyze data from patients with PBC and other liver diseases, with a level of sophistication not even dreamed of only 5 years ago. Laboratories within the Division of Liver Disease at Mount Sinai will make major contributions to improvements in molecular diagnostics and imaging for viral hepatitis and its fibrotic complications. This will reduce the need for invasive methods of assessing liver disease. Antiviral therapies for the treatment of hepatitis B and C will be continually refined, and will include new therapeutic tools such as ribozymes, in addition to improved versions of conventional antiviral drugs. Along with better characterization of genetic and host factors that influence prognosis and response to therapy, these will lead to improved outcomes for medical treatment of these serious illnesses. Improved understanding of the immunopathogenesis of PBC will permit the development of rational, successful medical therapy for this disorder as well. Basic studies of the membrane transport of fatty acids will provide insights that will foster specific therapies for steatohepatitis, as well as for disorders such as obesity and non-insulin-dependent diabetes mellitus, which are not primarily diseases of the liver. Antifibrotic therapies, already in early clinical trials, will be refined on the basis of still further understanding of the fibrotic process, and will delay the evolution of cirrhosis across a wide spectrum of liver diseases, even those for which the underlying pathogenesis is incompletely understood. These advances, in all of which Mount Sinai scientists will play a major role, will reduce the need for liver transplantation for many patients, thereby bringing into more reasonable balance patient needs and the limited supply of donor organs.

The progressive maturation of gene therapy will overcome current obstacles and achieve safe, targeted delivery and sustained function of a variety of genes. Isolated hepatocyte transplantation will also find a role in the treatment of genetic diseases of the liver and, perhaps, of some acquired forms of liver failure. These complementary modalities have the ability either to replace genetically deficient gene function or to augment acquired deficiencies of function, for a spectrum of disorders from fulminant liver failure to malignancy. These efforts will be informed by the knowledge of the human genome sequence in ways that cannot be predicted, and totally new paradigms of cellular and integrative biology are sure to emerge. Equally certain is that growth in biological understanding and therapy will dramatically enhance collaboration among Mount Sinai's programs in liver disease, neoplastic diseases, pediatrics, and genetics. Although these medical advances will decrease the need for liver transplantation, transplants will remain a crucial therapy of last resort. Transplantation biologists from the Immunobiology Center and the Transplantation and Gene Therapy Institutes, working in collaboration with the Division, will discover the optimal modes of immunosuppression that can prevent liver rejection and minimize complications. For desperately ill patients awaiting liver transplantation, new modalities will be developed as a bridge to liver transplantation, using either extracorporeal devices or molecular reconstitution of liver function. The Transplantation Institute will continue its pioneering role in creating new surgical options for patients requiring liver transplantation, as exemplified by the recent growth in living-related-donor transplantation surgery.

Underlying all these efforts will be the sustained growth in interdisciplinary science that is so vital to success in this golden age of biology, combining the expertise of basic scientists and clinicians in divisions and departments throughout the institution. This critical ingredient will create synergy in all aspects of science and clinical care. These activities, in turn, will continue to rely on the support of the NIH and other federal agencies, pharmaceutical partners, grateful patients and generous patrons. Now, as much as ever, the Mount Sinai Division of Liver Disease — together with its many institutional partners — is on course to maintain its role as a world leader in understanding and treating patients with liver diseases.

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The Mount Sinai Division of Gastroenterology at the Beginning of the 21st Century

Steven H. Itzkowitz, M.D.

Abstract

The Mount Sinai Division of Gastroenterology has an international reputation for outstanding contributions to the study of digestive diseases, especially inflammatory bowel disease. A discussion of the current structure of the gastroenterology (GI) fellowship training program is provided, along with an overview of the GI Division at the turn of the 21st century.

Key Words: Gastroenterology, The Mount Sinai Hospital, twenty-first century.

Introduction

The dawn of a new century is an appropriate time to survey the medical advances of the past one. The scientific community has just reported the sequencing of the human genome. The tremendous achievement of the Human Genome Project is a tribute to how rapidly scientific knowledge is advancing. Gene therapy may become a reality in the delivery of health care during this new century. It has been said that biological science's knowledge is doubling every 180 days (1). This exponential increase in scientific knowledge probably underlies the fact that half of the increase in the average life expectancy in recorded history occurred within the last century (2). Curiously though, most of this increase occurred in the first half of the old century. Advances in public hygiene and disease prevention, even more than medical interventions, account in large part for the rise in life expectancy from 47 years in 1900 to 78 years in 1995 (2). Preventive medicine has had a tremendous impact in some areas, such as infectious forms of diarrheal illness, although these remain a major cause of death in many underdeveloped countries.

The specialty of gastroenterology combats these and other diseases of the gastrointestinal system. Possibly its greatest single advance in the past century was the development of oral rehydration therapy for cholera, which was based on scientific understanding of the processes involved in intestinal absorption. The abundance of serious gastrointestinal diseases ensures a constant need for individuals trained in the specialty of gastroenterology and committed to advancing public health. This article will provide an overview of the current gastroenterology training program of The Mount Sinai School of Medicine.

Gastroenterology Fellowship Training

There are currently 250 gastroenterology (GI) residency (fellowship) programs in North America. In the mid-1990s, the duration of gastroenterology fellowships in the U.S. was extended from two to three years, in recognition of the growing complexity of the specialty and to provide sufficient time for fellows to pursue

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scholarly activity during their training. Reflecting the major scholarly disciplines within the specialty, the American Gastroenterological Association currently consists of 11 sections (Table 1). Although this structure was created partly for organizational purposes, it reflects the major areas of training and competence that are expected of modern gastroenterologists. Along these lines, the Gastroenterology Leadership Council (GLC) established a curriculum that attempts to standardize education of the gastroenterology trainee (3).

The three-year fellowship program at the Mount Sinai Division of Gastroenterology provides at least 18 months of clinical training. The remaining time is devoted to specialized research. The clinical training consists of consultative experience in both the in-patient and out-patient settings, learning how to perform endoscopic procedures, and training in hepatology (including the complexities of liver transplantation). The Mount Sinai GI Fellowship program presently includes experience on four campuses: The Mount Sinai Hospital, the Veterans Affairs Hospital in The Bronx, The Mount Sinai Services at the City Hospital Center at Elmhurst, and Queens Hospital Center. Thus, it exposes the GI fellow to a variety of patient populations and faculty expertise. There are currently 12 fellows in the program.

All fellows, as part of their training, are required to pursue either clinical or laboratory-based research (Table 2). The fellow selects a topic of interest and is paired with an appropriate faculty mentor, who helps to develop the line of investigation. In addition to personal mentoring, fellows attend institution-wide conferences and lectures that further develop their knowledge base. Fellows also have many opportunities to develop their public speaking skills at internal conferences, and by the end of their three-year fellowship, it is expected that all fellows will have presented their own work at local and national meetings.

A particular strength of the Mount Sinai Division of Gastroenterology is in the field of inflammatory bowel diseases (IBD). Training in IBD is facilitated by the availability of a large patient population with these diseases, and considerable depth of faculty in this area. Research in the field of IBD at Mount Sinai includes a rather comprehensive variety of topics, including basic immunopathogenetic mechanisms, genetic susceptibility, experimental therapeutics, research on classification and natural history of IBD, new surgical therapies for IBD, outcome measures (such as quality of life) and treatment of complications following ileal pouch anal anastomosis procedures, and basic mechanisms and clinical management of colitis-associated neoplasia. Fellows participate in these projects under the guidance of faculty mentors. In addition, a special one-on-one IBD preceptorship has been in place for many years. Under the supervision of a master clinician, this rotation has each senior fellow spending time learning the art of the consultation and gaining experience with ambulatory and in-patient gastroenterology. This valuable training experience, initially under the skilled guidance of Dr. Henry Janowitz (4), has more recently been supervised by other master clinicians, including Dr. David Sachar and Dr. Daniel Present. In 1999, Dr. Present established a new training opportunity for fellows from outside institutions to spend an intensive year of research and patient care devoted to IBD, with the goal of having this fellow return to his or her home program to further enhance its IBD program.

As part of their learning experience in consultative gastroenterology, all fellows receive superb training in endoscopic procedures. The chief of Endoscopy, Dr. Jerome Waye, is a highly gifted teacher, who along with a staff of highly proficient endoscopy faculty, personally supervises fellows in the indications and techniques of endoscopy.

Mount Sinai also has a strong tradition in the study of liver diseases (5), which led to the creation of a separate Division of Liver Disease. All gastroenterology fellows at Mount Sinai obtain outstanding training in hepatology. During the rotation on the Liver Disease ser-

TABLE 1

Sections of the American Gastroenterological Association

Biliary Disorders
Clinical Practice
Esophageal, Gastric, Duodenal Disorders
Gastrointestinal Oncology
Growth, Development and Aging *
Hormones, Transmitters, Growth Factors and their Receptors
Immunology, Microbiology and Inflammatory Disorders
Intestinal Disorders
Motility and Nerve Gut Interactions
Nutrition
Pancreatic Disorders

* As part of the Strategic Plan of the AGA to enhance research and education in nutrition, in the Year 2000 the Growth, Development and Nutrition section was renamed Growth, Development and Aging, and a new Nutrition section was established.

TABLE 2
Research Projects in the Division of Gastroenterology

Field	Topic	Principal Investigator(s)
	Basic Research	
Gastrointestinal Oncology	Pathobiology of mucins in GI cancer	Steven Itzkowitz
	Gene therapy of metastatic colon cancer	Steven Itzkowitz, Mark Babyatsky
	H. pylori in gastrointestinal lymphoma	Steven Itzkowitz, Lawrence Werther
Mucosal Immunity	Neuropeptides in IBD	Mark Babyatsky
	Epithelial cells in IBD	Lloyd Mayer
	Mucosal cytokines in IBD	Lloyd Mayer, Scott Plevy
	Genetic susceptibility to IBD	Scott Plevy, Lloyd Mayer
	Clinical Research	
Inflammatory Bowel Disease	Novel immunomodulatory agents/IBD	Daniel Present, David Sachar, Lloyd Mayer, Asher Kornbluth, James Marion, Ellen Scherl, Simon Lichtiger, Samuel Meyers, James George, Lisa Toy
	Ileal pouchitis — therapy, natural history	David Sachar, James Aisenberg
	Quality of life — outcomes research	Anthony Weiss
Gastrointestinal Oncology	Cancer in IBD	Steven Itzkowitz, David Sachar, Jerome Waye, Daniel Present, Peter Rubin, Thomas Ullman
	High-risk colon cancer registry	Steven Itzkowitz
	Neuroendocrine tumors	Richard Warner
Endoscopic Research	Colonoscopic tatooing	Jerome Waye
	Novel endoscopic cautery techniques	Jerome Waye
	Biliary endoscopy	David Jaffe
	Endoscopic ultrasound	Harry Snady, Thomas Riley, Anthony Borcich
	Ischemic bowel disease	James George
Motility Disorders	Spinal cord injury	Mark Korsten
	Gastric and small intestinal motility	Mark Korsten
	Collagen vascular diseases	Barry Jaffin
	Pelvic floor dysfunction; incontinence	Suzanne Rose
	Esophageal motility disorders	Lawrence Cohen
Irritable Bowel Syndrome	Combined medical/psychological therapy	Charles Gerson
	Novel probiotic therapies	Gerald Friedman

vice, they focus on the evaluation and treatment of patients with complex liver disease (pre- and post-transplant). The other three campuses feature unified GI/liver consultative experiences, affording additional training in liver disease. For the GI fellow with a particular interest in pursuing a career in hepatology, the third year of the three-year fellowship can be completely devoted to training in liver disease. In addition, the Division of Liver Disease offers a specialized fourth year of training.

As an integral part of fellowship education experience, the GI Division offers an extensive menu of teaching conferences (Table 3). In addition to these conferences, fellows rotating on the other campuses are exposed to separate pathology, radiology, and clinical conferences conducted on those campuses. While rotating on the Mount Sinai Liver Disease service, fellows attend conferences within the Division of Liver Disease, including liver pathology, ambulatory liver diseases, journal club and grand rounds. All GI and Liver fellows at Mount Sinai are expected to attend weekly Department of Medicine grand rounds, weekly GI/Liver Research Seminar and the bi-weekly Molecular Medicine/Dean's Lecture Series, which features outstanding scientists dis-

TABLE 3

Conferences in the Division of Gastroenterology

Conference	Description
1. GI Grand Rounds	
Summer Lecture Series:	This series of 10–12 weekly Friday morning conferences introduces fellows to basic and clinical pathophysiology and to fundamentals of managing the most common sites and categories of disease seen in GI practice.
Controversies in Gastroenterology:	Interdisciplinary panels discuss realistic cases of the commonest clinical problems in gastroenterology, exploring diverse viewpoints concerning the safest and most cost-effective approaches to prevention, diagnosis, and treatment.
Clinical Trends & Topics:	Clinical outcomes, complications, and quality assurance issues are discussed in depth, centering around real cases identified in quality review exercises. The Gastroenterology fellow prepares presentations of literature reviews and evidence-based conclusions in collaboration with the faculty moderator.
Fellow's Pathophysiology Seminar Series:	With a single thematic topic running throughout the academic year, each GI fellow chooses a particular aspect of the topic, researches it in depth, and presents a full and formal slide-illustrated lecture on it to the entire division. Fellows are supervised by a faculty mentor.
IBD Case Conference:	GI fellows present a patient with IBD who exemplifies a particular management problem. A multidiscipliinary panel discusses the medical, surgical, pathological, and radiological aspects of the case, followed by a literature review prepared by the fellow.
Invited Lectures:	Clinical and basic science topics are covered by speakers from inside and outside the Medical Center.
2. GI Endoscopy Conference	A weekly conference led by the chief of Endoscopy, highlighting interesting diagnostic or management problems. Videotapes are presented by gastroenterologists and laparoscopic surgeons.
3. GI Fellows' Endoscopy Conference	A weekly conference attended by GI fellows during which the chief of GI Endoscopy demonstrates lesion recognition, and discusses the latest innovative therapeutic endoscopic technologies and issues related to proper indications for performance of endoscopy.
4. GI Pathology Conference	A weekly conference at which fellows present their biopsies of the preceding week to the senior GI Pathology attending and other GI attendings for review and discussion regarding diagnostic and management decisions. Operative specimens and autopsy results are also presented and discussed.
5. Chief's Rounds	At this bi-weekly conference, fellows meet with the director or director emeritus of the division to present a noteworthy recent case. A strong emphasis is placed on the reading and interpretation of GI x-rays. Fellows are expected to provide literature that offers some insights into the clinical entity they are presenting.
6. GI Journal Club	A bi-weekly journal club is held, consisting of a topic-oriented approach to interpreting the medical literature and mastering the statistical methods. Statistical concepts and study design are addressed in detail through homework assignments at each session.
7. Ambulatory Care Conference	This bi-weekly conference immediately precedes Continuity Clinic. Fellows present one of their own clinic patients who manifests a particular management problem, and use an evidence-based medicine (EBM) approach to review the literature on the subject. A final management decision for the patient is then reached in conjunction with faculty.
8. Motility/Dysphagia Conference	A monthly conference that gives fellows an understanding of the indications and potential pitfalls in the performance of motility studies.
9. Pancreaticobiliary Conference	This monthly interdisciplinary conference brings together physicians and investigators from Gastroenterology, Liver Disease, Laparoscopic Surgery, Hepatobiliary and Transplant Surgery, and Diagnostic and Interventional Radiology to discuss interesting, problematic, and illustrative pancreatic and biliary cases.
10. GI/Liver Research Seminars	This weekly conference provides a forum for principal investigators from outside and within the institution to present research related to GI and liver disease.

cussing a broad range of clinical and basic science topics.

The GI Division is also responsible for undergraduate teaching programs. The first-year medical students are taught basic histology and anatomy of the GI tract by the Gastroenterology faculty in conjunction with faculty in the Department of Anatomy and Cell Biology. Second-year students receive an intensive, 6-week course on GI/liver pathophysiology, which integrates concepts of pathophysiology, diagnostic strategies, medical and surgical management, geriatrics, pediatrics, and bioethics. In addition to core lectures, case-based small group discussions are led by GI and Liver faculty. Medical students in third- and fourth-year clinical clerkships are expected to see and examine patients with gastrointestinal and liver diseases and interact with faculty preceptors, including those in Gastroenterology and Hepatology.

Leadership of the Gastroenterology Division of The Mount Sinai School of Medicine

In 1958, the Division of Gastroenterology was founded by Dr. Henry D. Janowitz, who served as its director until 1983. As a tribute to Dr. Janowitz's service to the GI Division and his international reputation, in 1992 the GI Division was officially endowed as the Dr. Henry D. Janowitz Division of Gastroenterology, becoming the first named GI division in the country.

In 1983, Dr. David B. Sachar became the second chief of Gastroenterology. Dr. Sachar was invested as the first Burrill B. Crohn Professor of Medicine in 1992.

Dr. Steven H. Itzkowitz assumed leadership of the Dr. Henry D. Janowitz Division of Gastroenterology on July 1, 1999, and was inducted as the second Dr. Burrill B. Crohn Professor of Medicine in September 1999. Dr. Itzkowitz, an alumnus of the Mount Sinai School of Medicine (Class of 1979) was recruited from the University of California at San Francisco, where he served as a GI fellow and subsequently as assistant professor of Medicine. He served as associate director of the division from 1993–1999, and is currently chair of the GI Oncology Section of the American Gastroenterological Association, and president of the New York Gastroenterological Association.

Faculty of the Division of Gastroenterology

The division's faculty currently consists of 50 physicians, including seven full-time gastroenterologists, representing a broad diversity of expertise. Faculty members contribute to the teaching program by mentoring GI fellows in research, supervising endoscopy, teaching fellows, medical residents and students on the consultation service and in the clinic, and participating in conferences.

Many of the currently active gastroenterologists have achieved international prominence and recognition for making major contributions in their area of expertise (see also Table 2). These include Jerome Waye (chief of Endoscopy; founder and developer of new endoscopic techniques), Daniel Present (developer of novel immunomodulatory therapies in IBD), J. Lawrence Werther (role of the gastric mucous barrier and *Helicobacter pylori* in acid peptic disease and gastric cancer), Mark Chapman (role of gastric acid secretion in peptic ulcer disease), Charles Lieber (alcoholic liver disease), Richard Warner (neuroendocrine tumors), Gerald Friedman (gastrointestinal pharmacotherapeutics and irritable bowel syndrome), Charles Gerson (physiology of the small intestine and irritable bowel syndrome), Samuel Meyers (medical therapy of IBD), Peter Rubin (endoscopic management of neoplasia in IBD), Simon Lichtiger (medical therapy of IBD), Mark Korsten (pancreatitis and gastrointestinal motility disorders), Blair Lewis (small bowel enteroscopy and endoscopic evaluation of gastrointestinal bleeding), Asher Kornbluth (medical therapy of IBD), Mark Babyatsky (role of neuropeptides in IBD and mucosal restitution), Lawrence Cohen (esophageal diseases), Barry Jaffin (gastrointestinal motility disorders) and Suzanne Rose (gastrointestinal motility disorders and medical education).

The Gastroenterology Service of The Mount Sinai Hospital

The Mount Sinai Hospital has more than 1200 beds, of which 600 are on teaching services. Two hundred of these are occupied by patients with gastrointestinal disease. The facilities include a new state-of-the-art pavilion designed by the famous architect, I.M. Pei, completed in 1992. In 1995, gastroenterology patients on both medical and surgical services were consolidated into an autonomous, integrated GI Care Center with its own dedicated teams of house staff and teaching attending physicians. Recently renamed the GI-Surgical Subspecialties Care Center (GISS-CC), it offers the benefit of centralized administration. Perhaps more important, it streamlines the delivery of nursing care and social service support by staff who are familiar with issues relevant to the GI patient (for example, adjusting to and caring for a new ileostomy). House staff in the Department of Internal Medicine rotate on the GI-Surgical Subspecialty Care Center for two months during their three years of internal medicine training and become familiar with the diagnosis and management of complex GI and liver diseases. During their rotation, they are supervised by a GI and a Liver attending whose primary purpose is to teach these residents. With teams of medical and surgical residents making rounds on the same ward(s), interaction between them is greatly facilitated. The Gastroenterology fellow assists the medical house staff with the management of GI patients, including any procedures that are indicated, and also functions as a liaison between the house staff and the Gastroenterology attending physician. To assure continuity of care, upon discharge from the hospital, any patient who does not have his/her own private doctor can be followed in the clinic by the Gastroenterology fellow who cared for him/her in the hospital.

In addition to caring for patients on the inpatient GISS-CC Teaching Service, Gastroenterology fellows are assigned to handle requests for consultations from other services in the hospital. Daily clinical records, consultations, and the performance of procedures during the three weekly endoscopy sessions are always under the supervision of an attending physician.

In the ambulatory GI clinic, new patients are seen by Gastroenterology fellows alone with those they have seen previously in the clinic or hospital. A separate Continuity Clinic is specifically designed for fellows to see their own cadre of patients, with whom they have established a relationship based on prior inpatient or outpatient care. The regular Mount Sinai GI clinics meet twice a week and are supervised by the same attending physicians throughout the entire year. The fellows have complete responsibility for their outpatients, who may call them for medical advice at any time.

Conclusion

Training in gastroenterology is becoming increasingly more complex and specialized, in keeping with rapid advances in medical knowledge and technology. We live in an exciting time, when sophisticated biotechnology can make a tremendous impact on how we treat, and even think about, disease. The application of new knowledge together with powerful molecular tools to treat and prevent digestive diseases should allow us to make an even greater impact on public health in the next century.

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Pediatric Gastroenterology at The Mount Sinai Hospital

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Abstract

The history of pediatric gastroenterology at Mount Sinai begins in 1960. Early publications by Drs. Korelitz and Gribetz on the management of inflammatory bowel disease in children served as the preface to forty years of progress in this important area. The history of pediatric gastroenterology includes important work by many individuals, including Horace Hodes, Lotte Strauss and Frederick Kopel. Early observations on the nature of inflammatory bowel disease (IBD), and its course, preceded work on nutritional therapies for IBD, mechanisms of gene-nutrient interactions, regulation of gene transcription, and molecular processes involved in bile transport in the liver and small intestine. Over the last twenty years, the division has grown in size and reputation. Today there are fourteen full-time faculty — 9 M.D.'s and 5 Ph.D.'s — who work in three funded research laboratories. There are also five advanced practice nurses (including three nurse practitioners), two social workers and two nutritionists, as well as several administrators and assistants. In addition to being recognized as a premier center for the treatment of children with general pediatric gastroenterological problems, especially inflammatory bowel disease, the division is also known as one of the nation's largest pediatric liver and liver transplant centers, and it is rapidly becoming one of the largest pediatric short gut syndrome and small bowel transplant centers.

Key Words: Pediatric gastroenterology, inflammatory bowel disease, liver disease, short gut syndrome, liver transplant, small bowel transplant, Mount Sinai.

Dr. Frederick Kopel was probably the first "official" pediatric gastroenterologist at The Mount Sinai Hospital, specializing in cystic fibrosis. In the 1960s, Kopel was encouraged by Drs. Fenton Schaffner and Hans Popper to learn and adapt the techniques of liver biopsy to pediatrics. Dr. Lotte Strauss, together with Popper, studied neonatal hepatitis and attempted to correlate what was seen histologically through the microscope with what was seen clinically and biochemically. Kopel also joined Burton Korelitz and Donald Gribetz to publish a major report on granulomatous colitis (1). This work emphasized the importance of appropriate medical management for granulomatous disease, in contrast to the recommendations for surgery in ulcerative colitis.

Inflammatory Bowel Disease

Korelitz and Gribetz were struck by the devastation that resulted from inflammatory bowel disease (IBD) in children. They systematically examined the natural course of IBD in the pre-steroid era and mentored one of their residents, Dr. Irwin Danziger, as he sought answers to important questions in pediatric gastroenterology. Korelitz, Gribetz and Danziger reviewed the records of children with IBD followed at that time by Korelitz and seen at Mount Sinai (2). They noted that, in the era before anti-inflammatory drugs, most children seen in the hospital became very ill, and many died. Anecdotal reports relate many animated discussions between Dr. Horace Hodes, the then-chief of pediatrics, who staunchly advocated medical management, and the well-known surgeon, Dr. John Garlock, chief of one of the surgical services. Drs. Garlock and Ginzburg usually favored surgical management. Danziger's review of the records suggested that if a child survived for two years after being hospitalized for severe colitis, not only was that child very fortunate, even remarkable, but that even after the two years the child might still become very ill. His review of patients with ulcerative colitis supported the surgical approach advocated by Garlock. Although this preemptive operative approach for these children was seriously criticized, Ehrenpreis concluded that a child with severe, acute colitis should be made as well as possible, and that the colon should be removed early in the course of the disease (3).

The work by Korelitz, Gribetz and Danziger reflects the highest level of pioneering work in

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pediatric gastroenterology. Their studies of the prognosis of ulcerative colitis with onset in childhood in the pre-steroid era are historic. To quote from their discussion (2), "the relentless morbidity menacing the child with ulcerative colitis is given somber testimony by this study of the history of the disease in the pre-steroid era." Korelitz, Gribetz and Danziger (2) also reported that 43% of the children who developed ulcerative colitis in the pre-antimicrobial era died as a result of their disease, the mean age of death occurring at 22 years. After the development of antibiotics, that mortality was cut in half, but was still 22%, with a mean age at death of 17 years. The article, which detailed the complications and long-term follow-up, is a landmark in the study of pediatric inflammatory bowel disease. The companion paper by Korelitz and Gribetz on the prognosis of ulcerative colitis with onset in childhood, in the steroid era (4), was also important. They reported that with the use of adrenocorticotrophic hormone (ACTH) and adrenal steroids, the number of complications from ulcerative colitis (inflammatory bowel disease) has "not been obviously reduced." The number of patients with ulcerative colitis treated by surgery increased during the early years of this period, and surgery seems to have been performed when the patients were less ill. This reduction in urgent surgery seems to have been accompanied by fewer operative stages and fewer operative complications in morbidity and mortality. After six years of disease, 30% of the patients had ileostomies, but almost 90% were alive and 40% were well without definitive surgery. The authors concluded that the response to steroids helped determine which children with inflammatory bowel disease would benefit from colectomy. They concluded that surgery should be performed early enough to avoid irreversible complications of the disease and to minimize surgical mortality.

The Mid-1970s

Events occurring in the mid-1970s (1973–1974), while Horace Hodes was Chairman of Pediatrics, confirmed the significance of some of his earlier findings from the 1940s. Hodes, while studying diarrhea in calves, had found a filterable (viral) agent that could not be identified with the existing technology; stool samples were frozen for future investigation. Years later, with the use of electron microscopy, it was discovered that the viruses he had isolated, but not identified, belonged to the same family of viruses that was found to cause infantile winter diarrheas, i.e., rotavirus (personal communication).

In 1975, Gribetz and Korelitz worked with another Mount Sinai pediatric resident, Dr. Michael Berger, to report their findings of growth retardation in children with ulcerative colitis, and the effects of medical and surgical therapy (5).

After Kopel's untimely death, in 1971, Dr. Richard Bonforte helped fill the void. He worked with the then-chief resident, Dr. Neal LeLeiko, to re-establish the sweat test as the procedure for diagnosis of cystic fibrosis. Bonforte established the Cystic Fibrosis Center and the Pediatric Pulmonary Center. LeLeiko went on to the Massachusetts Institute of Technology, where he earned his Ph.D. in nutritional biochemistry and metabolism in the laboratory of Dr. Hamish Munro. He then went to the Boston Children's Hospital to train in pediatric gastroenterology, following which he was recruited (in 1979) by Dr. Kurt Hirschorn, Chairman of Pediatrics, at Mount Sinai, to establish a major division of pediatric gastroenterology.

LeLeiko's expertise was in nutritional metabolism and the use of parenteral nutrition and special feeding regimens to treat children with a variety of diseases, especially inflammatory bowel disease and short gut syndrome. He rapidly established Mount Sinai as a major referral center for children with both ulcerative colitis and Crohn's disease, and his interest in nutritional metabolism led to published papers on energy expenditure in patients with Gaucher's disease (6), inflammatory bowel disease (7), and also in elderly Alzheimer patients (8). LeLeiko, along with Dr. Martin Walsh, studied the use and effects of 6-mercaptopurine on intestinal metabolism and found that often the effects of 6-mercaptopurine could be biochemically mimicked by the use of an elemental diet (9). LeLeiko trained many pediatric gastroenterologists, some of whom have remained at Mount Sinai. Dr. Keith Benkov, for example, became a recognized clinical consultant of the division's clinical practice in caring for children with inflammatory bowel disease. Benkov was invited to discuss the case of a child with inflammatory bowel disease for the case records of the Massachusetts General Hospital (10).

LeLeiko's interest in short gut syndrome and nutrition has continued to develop, and 1999 saw the successful inauguration of the region's first small bowel transplant program.

Patients whom LeLeiko had been following, and who in past years had been sent to other centers, could now receive all of their care at Mount Sinai.

Of the 26 fellows trained in the division, 8 are now division chiefs and directors elsewhere, 8 are full-time academic pediatric gastroenterologists, 2 full-time laboratory researchers and 8 pediatric gastroenterologists in private practice. The members of the division, under LeLeiko's leadership, continue to see children with inflammatory bowel disease and attract a large number of children with nutritional problems, especially children with short gut syndrome and liver disease

In 1990, the existence of the division's significant liver program was instrumental in New York State authorizing the liver transplant program at Mount Sinai. The pediatric portion of the liver transplant program has developed into one of the major pediatric liver transplant programs in the country. Two of LeLeiko's fellows, Drs. Audrey Birnbaum and Joel Rosh, developed a particular interest in liver diseases and liver transplant, and they helped guide the program through its nascent years. In 1997, Dr. Birnbaum reported, with the rest of the group, on the recurrence of autoimmune hepatitis after liver transplantation (11), thus revising the then accepted view that the disease did not recur. In 1996, Dr. Frederick Suchy, a world-renowned pediatric hepatologist, was recruited as Chairman of Pediatrics. Dr. Benjamin Shneider was recruited from Yale to be director of the division's section for liver diseases.

Current Research

The division has had an active research program. The focus of the work by Walsh and LeLeiko has been on mechanisms of gene transcription in epithelial cells. Research has also focused on the study of gene regulation in the developing and differentiated epithelium and the special effects of nutrition on intestinal epithelium. The current goal of the laboratory is to understand the mechanisms of transcriptional control in epithelial cells. The division's studies have identified transcription factors and cofactors involved in the regulation of the cystic fibrosis transmembrane conductance regulator (CFTR) and N-myc genes. The studies have provided evidence for the function of transcription factors, mediated by protein kinase A and cyclic adenosine monophosphate (AMP), in the modification of chromatin structure and gene transcription. Discovery of a unique member, epithelial cell DNA binding factor-α (ECDFα), of the paired-homeobox class of transcriptional regulatory proteins encoding guanosine triphosphatase (GTPase) activity, has helped our understanding of the importance of these proteins in directing transcription through a GTPase-activated pathway. Analysis of these factors has also helped clarify the role of specific transcription factors in determining the fate of differentiating epithelial cells during development and oncogenesis. Many original research publications in prestigious scientific journals have resulted from this work (12–18). The group has also made significant contributions in this area, in the form of chapters in standard texts and reviews in specialty journals (19–22).

Suchy, working with Drs. M. Ananthanarayanan and An-Qiang Sun, focused on the ontogeny and regulation of bile formation, using the rat as an animal model. Since arriving at Mount Sinai they have focused on Na^+ taurocholate co-transporting polypeptide (ntcp) (NTCP in humans) gene, whose product is involved in the Na^+-dependent uptake of conjugated bile acids from sinusoidal blood into the hepatocyte across the basolateral membrane. They have successfully mapped and localized the chromosome in rat and mouse, and are working on mapping the human gene. In addition, they are in the process of generating transgenic mice that carry promoter regions for ntcp with a reporter gene whose activity can be assayed as an index of promoter activity. Effects of hormones, cytokines, or other agents on the activity of ntcp promoter are of great interest. Studies are in progress using the latest molecular techniques to create "knockout mice" in which the ntcp genes have been deleted. The laboratory also investigates a gene called "sister to p-glycoprotein (spgp) gene," which has been shown to be an adenosine triphosphate (ATP)-dependent bile acid transporter on the canalicular membrane of the hepatocyte, its human homolog has been found to be mutated in PFIC-2 (Progressive Familial Intrahepatic Cholestasis Type 2). The work at Mount Sinai has already resulted in several important contributions to the literature (25–29).

The primary focus of Shneider's research has been to elucidate the regulatory mechanism(s) associated with the ileal sodium-dependent bile acid transporter, including molecular events involved at the developmental and transcriptional levels. Descriptive studies of the response of this system to changes in bile acid homeostasis are also being undertaken in a variety of animal species, including rat, rabbit, and mouse. Other activities include analysis of bile acid transport proteins in acquired human liver disease and in previously poorly understood inherited pediatric liver diseases (28 – 32).

In 1998, more than 43 students and residents came from 10 medical centers and 6 medical schools to spend time at Mount Sinai. The Division of Pediatric Gastroenterology, with three funded laboratories, consists of 14 faculty (9 M.D.'s and 5 Ph.D.'s), three nurse practitioners, two social workers, three nurses, two medical assistants, and two nutritionists. Each year, approximately 4,000 patient visits are made to the doctors of the division.

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The Evolution of Gastrointestinal Endoscopy at The Mount Sinai Hospital

Jerome D. Waye, M.D.

Abstract

Gastrointestinal endoscopy came to The Mount Sinai Hospital in the 1950s, along with the Wolf-Schindler gastroscope. In 1961, it was supplemented by the Eder-Hufford semi-flexible esophagoscope and later by the Olympus gastrocamera and then the Hirschowitz fiberoptic instruments from ACMI and Olympus. A formal training program was started by Jerome Waye in 1966 for flexible gastroscopy and esophagoscopy. In 1969, endoscopic retrograde cholangiopancreatography (ERCP) was introduced. Colonoscopy was at first performed under x-ray control, and subsequently replaced by the nonfluoroscopic method of colonoscopic topography, which was developed by Dr. Waye. A full-time nurse who was in charge of the endoscopy unit founded the Society for Gastrointestinal Nurses and Assistants while working at The Mount Sinai Hospital.

Key Words: Endoscopy, esophagoscopy, gastroscopy, ERCP, colonoscopy, Mount Sinai Hospital.

GASTROINTESTINAL ENDOSCOPY came to The Mount Sinai Hospital in the 1950s, when Dr. Albert Cornell personally purchased the first Wolf-Schindler gastroscope (1). The instrument permitted gastric visualization via a series of lenses in the distal half; "flexibility" was achieved with a gentle curvature of 20% from a straight axis. Dr. Harry Yarness introduced the procedure to Mount Sinai after visiting Dr. Schindler and learning it from him. During residency training, Dr. J. Lawrence Werther, who was already interested in gastric physiology, extended his interest to upper intestinal endoscopy and became a teacher of gastroscopy along with Dr. Yarness.

At that time, rigid sigmoidoscopy and proctoscopy were being performed at Mount Sinai by surgeons and gastroenterologists, in a separate operating room (OR) within the ear, nose and throat (ENT) operating room suite. But gastroenterologists were not allowed to perform esophagoscopy, because the ENT service (whose OR was used by Gastroenterology) considered the esophagus to be within their domain. However, the ENT physicians permitted gastroenterologists to use the Wolf-Schindler gastroscope because its optics were fixed at a right angle to the long axis of the instrument, thus rendering it impossible to see the esophagus as the scope was passed through to the stomach.

In 1961 an Eder-Hufford (semi-flexible) esophagoscope was purchased by the Gastroenterology Division. The flexible portion consisted of a coil-spring obturator which passed through the long, rigid esophagoscope and protruded about 7 inches, thereby providing a short, flexible introducer to the otherwise inflexible instrument. The semi-flexible esophagoscope was introduced into the esophagus in a manner similar to that of the gastroscope, with the flexible portion advanced into the posterior pharynx by bending the coil spring with the fingers of the left hand, which had previously been inserted into the mouth. The right hand then swung the rigid portion around as the chin was extended to configure the mouth and esophagus in a straight line. During the procedure, the patient was supine on an examining table, with the head hanging over its edge, permitting the head-holder assistant to swing the head down to allow a straight intubation passage. The operator sat on a stool facing the patient. At the proximal end of the esophagoscope was a small telescope which could be rotated into view after the "flexible" obturator was withdrawn. This telescope focused on and magnified the tissue at the distal end of the esophagoscope. Esophagoscopy without the telescope, as performed by ENT physicians, displayed a tiny patch of mucosa 12 mm in diameter, viewed by the naked eye through a hollow tube 50 cm long. Because of

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the constraints imposed by the ENT Department, it was not possible to use this new, semi-flexible esophagoscope in the ENT operating room suite, and its use was confined to the GI clinic. Despite the magnified field visualized with the newer instrument, the ENT Department continued to do standard rigid esophagoscopy.

Preparation for an upper endoscopy was a formidable task. The ENT physicians taught gastroenterologists how to use cocaine to swab the posterior pharynx, providing effective local anesthesia. The pledgets of cocaine-laden cotton balls would be placed on an L-shaped clamp which painted the tongue and soft palate, gradually advancing deeper and deeper into the pharynx, where the swab, continually refreshed in a container of cocaine, would finally come to rest in the vallecular spaces. When the patient no longer retched on having the pledget placed deep into the pharynx, he or she was considered to be adequately anesthetized. Topical anesthesia was applied in a room across the hall from the main operating rooms, and following pharyngeal anesthesia, patients would walk across to the operating theaters, where rigid gastroscopy was performed without sedation. The Schindler rigid gastroscope had a two-inch rubber finger at the tip of the instrument, which aided its passage through the posterior pharynx. Hyperextension of the neck was accomplished as the gastroscope was introduced, because it was fairly rigid and an absolute straight path was necessary to be able to pass the scope from the incisor teeth to the stomach. Once past the cricopharynx, the instrument was rapidly advanced into the stomach. If the esophagus needed to be inspected, the ENT department was requested to perform esophagoscopy.

Light from a tiny bulb at the end of the gastroscope was transmitted through a series of lenses to the operator's eye. Neither fiberoptic teaching attachments nor video monitors were available, and the only view that could be obtained was through the lens at the proximal end of the scope. Since everyone in the room wanted to see any lesion found by the examiner, and photography had not been adapted to these instruments, the endoscopic examination necessarily took a long time when an abnormality was seen. During training sessions, each observer had to line up and take a quick look through the eyepiece as it was being held by the endoscopist. When more time was needed to see the mucosa, to view a lesion or to inspect the stomach, the endoscopist would take a stance in front of the patient, holding the protruding portion of the instrument with both hands, while raising both elbows to ear level. This maneuver would keep others from grabbing the scope during the examination. Since patients were not medicated for the examination, it had to be done as quickly as possible to minimize the discomfort. While endophotographs were unknown, sketches were commonly made of any lesion seen. The duodenal bulb was never visualized, and a complete view of the stomach was rare. Atlases of endoscopy were not available, but attending physicians and students pored over the drawings from the Schindler book of endoscopy (2), which was considered the gold standard.

In 1975, the ENT Department left the operating theaters in the old administration building and moved to new quarters. The Gastroenterology Division was assigned to these vacated suites and was then able to perform both esophagoscopy and gastroscopy without supervision by the ENT Department. Soon, a new "system" was devised, with which esophagoscopy and gastroscopy could be performed sequentially. After completing the inspection of the esophagus with a standard Eder-Hufford esophagoscope, a slim-caliber lateral-viewing gastroscope could be passed through the esophagoscope to inspect the stomach. This modified system was the Eder-Palmer trans-esophagoscopic semi-flexible gastroscope.

The division later obtained a gastroscope with a channel for a small forceps, to allow for taking a biopsy. This was known as the Benedict operating gastroscope, manufactured by the American Cystoscope Makers, Inc. (ACMI), of New York City. When the forceps was extended beyond the gastroscope for only a few centimeters, it passed out of the field of view. In order to accomplish a biopsy, the forceps had to remain in the field of view while suction was applied to deflate the stomach. As the stomach collapsed and the lesion occluded the view, the biopsy forceps were closed and then withdrawn. Thus, adequate biopsies were obtained mainly by chance.

During both gastroscopy and esophagoscopy, air had to be continually insufflated by a hand-held bulb which was pumped throughout the examination. The operator would often hold the bulb in the palm of the hand, pumping it with three fingers while the thumb and forefinger held onto the shaft of the gastroscope to steady, advance, or rotate it.

It was during my fellowship, in 1963, that Hirschowitz's first flexible fiberoptic instrument became commercially available from ACMI. Dr. Gerald Friedman and I, co-fellows, carried this fiberscope from floor to floor, showing the house staff and attending physicians the new instruments for performing upper intestinal endoscopic examinations. The first instruments were side-viewing scopes that did not permit a view of the esophagus, but a dedicated forward-viewing instrument soon followed. Focusing had to be done continually, and, as with rigid scopes, air was pumped in with a hand-held insufflator. The light source was actually a small incandescent bulb located at the tip of the instrument, causing the distal end of the gastroscope to become rather hot during prolonged examinations. The fiberoptic bundles, which transmitted the image, were fragile, and if the scope became kinked (or, worse yet, was bitten), the broken fiberoptic bundles were immediately seen as permanent black spots in the visual field.

Drs. Yarness and Werther, the previous teachers of rigid endoscopy, each held a training session one day a week. In 1963, when the flexible tools became available, they included them in the regular schedule of cases. When I finished my fellowship in 1963, I had performed flexible endoscopies twice weekly under supervision, and had twice the expertise with these instruments as the instructors, who only used the flexible scopes once per week. I was requested to stay on as a teacher of flexible endoscopy. Soon, Dr. Werther resumed his laboratory activities on gastric acid secretion and Dr. Yarness retired, leaving me as the only (very young) teacher in the endoscopy unit. Dr. Julius Wolf, who was chief of staff of The Medical Service at the Bronx Veteran's Affairs (VA) Hospital, was enlisted to come to Mount Sinai twice a week to be the official head of the endoscopy unit and lend an air of authority (and maturity) to endoscopy. Dr. Wolf came to Mount Sinai on a regular basis for three years and then on an irregular basis for another year, until 1972. At that time, I found myself the senior gastrointestinal flexible endoscopist. I was never officially appointed to the position of chief of GI endoscopy, since this program was always considered to be an integral part of the overall GI program.

Changes in techniques and instrumentation progressed at a dizzying pace. Just before the introduction of fiberoptics, miniaturized photographic capability was integrated onto the tip of a flexible endoscope. The first flexible gastroscopes were "blind," without visual capability, but had a camera on the tip. This gastrocamera took multiple pictures on a 5-mm film strip, which, upon development, showed the mucosal views taken during a prescribed sequence of instrument positions while moving the patient from supine to prone. Mount Sinai did not acquire the original 1962 gastrocamera, but did buy the next model, GTF V, manufactured by Olympus Optical Company, Japan, which provided both a fiberoptic view and a film strip. The tiny images were projected onto a small screen, and our weekly endoscopy conference was born, as the growing number of faculty and GI fellows met regularly to watch the showing of the week's work. When endoscopic retrograde cholangiopancreatography (ERCP) was introduced, I traveled to Japan, in 1969, to learn the various techniques. Upon returning to Mount Sinai, I asked a senior endoscopist from the Minneapolis VA hospital, Dr. Jack Vennes, to visit Mount Sinai and take me through ERCP procedures under his tutelage. There was no funding for this. I lined up a series of private patients and sent Dr. Vennes the full amount of the fees collected from each patient to provide an honorarium and travel expenses. Once adept at this procedure, I traveled to several hospitals in New York City to teach the technique to anyone who asked.

When colonoscopy began at The Mount Sinai Hospital, it was performed under radiologic guidance, so that the location of the endoscope tip and the direction in which the endoscope was heading could be determined. The colonoscopes of that time had only two-way tip deflection and were rather stiff and clumsy. The first colonoscopic examination at The Mount Sinai Hospital was performed, without sedation, in the Radiology Department. Dr. Bernard Wolf, the then-chief of Radiology, and the other senior radiologists, were wondering how the advent of colonoscopy might affect the future need for the barium enema. At the onset, the patient was dismayed because of the gallery of attending radiologists, radiology fellows, attending gastroenterologists, GI fellows, and many x-ray technicians. She was also audibly uncomfortable during most of the procedure. After the first hour, all the attending radiologists had left, happy in the knowledge that this technique would not replace barium. After the second hour, all the GI attendings and fellows in Gastroenterology and Radiology disappeared. After the third hour, there was not a technician left to help with the imaging. Throughout the entire prolonged procedure, the patient, although obviously uncomfortable, continually encouraged and prayed for all the doctors. The procedure was successfully concluded, to the relief of both the patient and her endoscopist.

The following day, Dr. Wolf called me into his office and told me that I would not be able to tie up an x-ray room for half a day trying to perform colonoscopy. Eager to continue developing my skills in this examination, I asked Dr. David

Dreiling, a surgeon with an abiding interest in pancreatic physiology, if I could use his fluoroscope (with which he positioned his "Dreiling tube" for pancreatic secretory studies). His laboratory was on the sixth floor of the old hospital building and was not air conditioned. It was accessible by a stairway from endoscopy on the fifth floor level; the patients and I walked up and down the stairs to use this facility, since it was easier and quicker to walk with the patient and instruments rather than wait for the old elevator. My colonoscopy career began in the heat of midsummer and with a fluoroscope which was old and inefficient. One needed to dark-adapt for twenty minutes with red glasses in order to visualize the faint image on the screen, and, even so, if a hand was waved under the fluoroscopic screen, one could not discern the skeletal structures. Also, the shape of the instrument could be seen, but the air column was not visible.

During these tedious sessions, where sedation was not used, I noticed that various areas in the colon had different appearances and shapes that could be correlated with the position of the instrument tip as noted on the fluoroscopic screen. After four sweat-soaked sessions in Dr. Dreiling's fluoroscopy room, I decided that there had to be a better way of doing colonoscopy than with x-ray imaging. This experience stimulated me to develop the nonfluoroscopic method of colonoscopic topography by noting various visual landmarks in the colon, which give a fairly accurate location of the tip of the endoscope. Over the next few sessions, I was able to further delineate these landmarks and they became universally adapted (3). Currently, with the use of these landmarks, abdominal pressure, and palpation, most colonoscopy is currently performed without x-ray imaging.

The original GI endoscopy service consisted of three (previous ENT) operating rooms and the operating room office. The fluoroscopic unit for ERCPs was borrowed from a nearby surgical intensive care unit (ICU), so that all ERCPs were performed in the surgical ICU area. The first full-time nurse for GI endoscopy was Marna Schirmer, who was instrumental in teaching everyone how to do endoscopy. She formed the Society for Gastrointestinal Nurses and Assistants (SGNA) while running The Mount Sinai Hospital endoscopy unit. This organization is now the largest and best-known organization of its type in the world.

In preparation for the new Guggenheim Pavilion, it was necessary to demolish the building in which the endoscopy unit was located. Endoscopy was moved into the Annenberg Building, in a space that was known to be inadequate. Since it was the only space available, we were asked to "squeeze in" for a period of "one to two years," until the new building was constructed. That was fifteen years ago. The entire endoscopy space (as of this writing) is still contained in a 1,000 square foot area, which includes a waiting area, a reception area, a recovery space, two small endoscopy rooms, an even smaller storage room that was converted into a third endoscopy room, and a cleaning area. ERCPs are performed at a remote location using a C arm portable fluoroscope and monitor without the capability for overhead x-ray films. The unit currently performs about 7,000 endoscopic examinations annually. Because of space constraints, the forty members of the voluntary staff of the Gastroenterology Division now perform endoscopy in their private offices outside the hospital, while the full-time staff physicians have their own endoscopy set-up in their faculty practice area.

Many instructors are present for each and every scheduled endoscopy session. There is a special "fellows' endoscopy teaching session" weekly, in addition to the weekly "endoscopy conference." The latter has become one of the hospital's favorite meetings, attended by adult and pediatric gastroenterologists, general, laparoscopic and transplant surgeons, pathologists, residents, and medical students. This conference evolved from the original weekly gathering of interested GI physicians who reviewed the week's film strips of gastroscopic photographs.

The endoscopy training program at Mount Sinai is one of the best in the country, supervised by many dedicated GI attendings who give their time and effort without recompense. At the end of their training, the GI fellows are highly focused on both the cognitive and procedural aspects of endoscopy.

Plans have again been drawn up for a new endoscopy suite in the future ambulatory surgical pavilion, with an interim expansion and renovation of some of the current space.

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Ileostomy and Colostomy Support Groups

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Abstract

The first organized ostomy support group in the world was formed at The Mount Sinai Hospital, in 1950, through the efforts of a surgeon and the patients themselves. Later, similar groups were set up in other locations and some even took the name of Mount Sinai's first such society (QT).

These groups had two major functions:

- Psychological: reassurance and understanding from other ostomates before and after the operation; advice on how to deal with oneself and others.
- Educational: instruction on the details of stoma management; information for surgeons on the proper location and other details of fashioning a stoma; information to the public on the existence and needs of ostomates.

In order to extend services to more people and with more individual attention, a special clinic was established at The Mount Sinai Hospital devoted entirely to patients with ileostomy and colostomy. It too was the first of its kind anywhere.

Years later, two surgeons arranged an all-day convention of the ostomy groups in the greater New York City, New Jersey, and Connecticut areas, at the New York Academy of Medicine. At the convention, the idea of a national society was conceived. In the following years — in Detroit, then Cleveland, and finally Los Angeles — the United Ostomy Association was developed, structured, and incorporated.

The educational uses of the ostomy groups were later supplemented and partly replaced by enterostomal therapists who originally were trained and practiced in Cleveland. Now the therapists, the societies, and the ostomates themselves are available to patients with various types of stomas, whether recent or longstanding, before and after surgery.

Key Words: Ileostomy, colostomy, patient groups.

In 1949, four patients with ostomies met at the Veterans' Hospital in Valley Forge, PA, as did others in 1949 and 1950, in New York City and elsewhere. But these were occasional, spontaneous, mainly social get-togethers of two, three, or four persons with ileostomies or colostomies. The first formal, organized ostomy support group in the world began at The Mount Sinai Hospital in 1950; in 1952 I reported the earliest meetings of this group (1). The monthly meetings were attended by patients who had had ileostomies for the treatment of ulcerative colitis on the ward surgical service and other services, and at other hospitals. The meetings had their origin in a small social gathering at the home of one of the eight women patients who had come to know each other as patients in the hospital. It became clear that these patients had a most valuable idea which needed some nurturing. Both Miss L.M. Neary, a social worker assigned to the surgical service, and I set out to encourage these efforts.

Since the patients were admitted to Wards Q and/or T, the new group called themselves "QT Alumni." The choice of the term "QT" avoided using the word "stomas." Elsewhere, other groups began to form. For instance, in recognition of the fact that the pioneering work was done in New York, the Boston group called themselves QT Boston and the Detroit group, QT Detroit. Years later, people no longer felt it necessary to use the term "QT" and groups became known as ileostomy, colostomy, or ostomy associations (2).

In a 1987 interview with Hall (2), I described how I helped supervise the early meetings. My chief, Dr. John Garlock, was most helpful and encouraging. Because of his influence in the hospital, I was able to get support that I might not have gotten otherwise. My colleagues and co-workers, and others in the institution, were also favorably impressed. Ultimately, the group became larger and began to function by itself.

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Shortly after we started the ileostomy group, I thought we ought to start doing the same for people with colostomies. The first colostomy meeting, however, was discouraging. In the ileostomy group, there were a couple of very enthusiastic and remarkable young women and men who took responsibility and helped make the group possible. Unfortunately, the colostomy group did not have enough members willing or able to do likewise. Therefore, I didn't have another meeting until some years later, when three patients with colostomies met with my surgical colleague, Dr. George Schreiber, and me. They said that they wanted to form a group which included people who were willing to become involved (2).

The benefits derived by the patients in The Mount Sinai Hospital groups and elsewhere may be classified as psychological and educational.

Psychological. Enormous reassurance and support was received by the interaction of individuals with the same conditions, when they had the chance to discuss their feelings and how they dealt with family, friends, fellow-workers, and society at large. Also, the experiences of ostomates were enlightening to each other, notably on sex, pregnancy, occupation, and leisure activities. Patients have frequently said that their entire attitude changed when they were visited in the hospital by a club member. Some who had been unable or reluctant to properly manage their own stomal care after leaving the hospital came to accept their involvement in their own care. Moreover, even the well-adjusted person of long-standing club membership found an added meaning to his or her life by serving as an "expert" to help the neophytes (1).

Among the most useful contributions were visits by an ostomate member to patients before and/or after operations. Patients often reported that these visits transformed uncertainty to optimism. Instead of fear of "abnormality" because of the stoma, patients cheerfully adapted to a procedure which restored their health.

Educational. Information and even instruction on the management of ileostomy, colostomy and urostomy were provided by fellow patients, as well as by doctors and nurses who came as guests or advisers. Details were also provided about the specific types of appliances available, and the advantages and requirements of each. Before the advent of enterostomal therapists (ET), this technical advice was sometimes the principal source on which the ostomate could depend, since many doctors and nurses had limited experience in the details of stoma care and control.

Both patients and surgeons learned much at these meetings. For instance, the patients' recital of difficulties often indicated to the professional how to plan the stoma and its location before the operation, by taking into account particular anatomical and functional requirements of each person. When the enterostomal therapists came upon the scene, the needs of particular people and the resolution of difficulties were highly instructive to all parties. Moreover, the local groups working together could educate and influence the public, whereas individual patients, concerned about their privacy, were less likely to "reach out."

The Intestinal Rehabilitation Clinic

The ostomy group at Mount Sinai originally met in the evening in a clinic waiting room. Various problems were discussed, and then I, or somebody else, would talk. At the end of the meeting, the people would line up, and I would discuss their particular problems, one by one. I was joined later in this enterprise by Dr. George Schreiber, who had been a resident at Mount Sinai and then an attending (2, 3).

Attendance at meetings of the ileostomy club was about 15 at first; then it increased to more than 50, and sometimes to well over 100. The colostomy group, which met separately, also grew rapidly, making it impossible to deal with the special problems of individual people. In the late 1950s, I appeared before a committee of the Board of Trustees, headed by the president, Joseph Klingenstein, to request a special clinic devoted entirely to persons with external intestinal stomas. Soon afterward, the Trustees agreed. This "Intestinal Rehabilitation Clinic" was the first of its kind in the world. It was staffed voluntarily by myself, Dr. George Schreiber, Dr. Bernard Robinson, and Dr. Robert Turrell, a proctologist who would later found the Society for Surgery of the Alimentary Tract (at first, it was named the Society for Colon Surgery). A registered nurse, Miriam Jacobson, who was Robinson's office nurse, acted as the clinic nurse.

At that time, there was no clinic other than the one at Mount Sinai devoted solely to the care of stomas. At the Massachusetts General Hospital in Boston, and at other sites, there were follow-up clinics used by the surgical staff just to keep track of the postoperative patients.

The United Ostomy Association

In 1956, QT New York invited the known existing ileostomy and colostomy groups to share their experiences. Representatives from eight ostomy groups (six ileostomy and two ileostomy-colostomy) throughout the U.S. met there. Some attended with the idea of forming a national organization (4).

As a result of this meeting in New York, *Ileostomy Quarterly* and *Colostomy Quarterly* were created. The colostomy publication appeared only once, but the *Ileostomy Quarterly,* sponsored by QT Boston and edited by Edith Lennenberg, continued on a regular basis. In New York, Leon Berger put together a monthly bulletin, *QT New York,* which was mimeographed. Later, formally printed monthly bulletins were sent out by both the ileostomy group and the colostomy society.

In 1960, QT New York sponsored a workshop at the New York Academy of Medicine, to which all existing ostomy groups in the U.S. and Canada were invited (2, 4). There were presentations by patients and panel discussions by surgeons, internists, gastroenterologists, and psychologists. Afterwards, the people who came from the various clubs sat down with us and asked if it was possible to make something of this that extended beyond just the local area. We all thought it was a very good idea.

In 1961, a meeting was held in Detroit. I could not attend, but I was in touch by telephone with several people there, and learned that there was intense disagreement. I remember sending a telegram to one attendee, saying that if the thirteen colonies could get together and form a union, I hoped that people who had a common purpose could act together and forget geographic differences and other personal needs. I do not know whether the telegram had any effect at all, but I do know that the decision was made, at that meeting, to meet in Cleveland subsequently. During that interval, various working parties met to facilitate the founding of the new national organization (2).

At the Detroit meeting, a committee on a constitution and bylaws had been established. In 1962, delegates from 24 groups assembled in Cleveland, Ohio and set up the structure for the United Ostomy Association.

In Los Angeles, in 1963, the organization was officially and legally established and its first officers elected. *The Ostomy Quarterly* appeared in December 1963, under the editorship of Virginia Pearce — who introduced the term "ostomate" into the medical literature, taking it from Egon Orawan, an engineer at MIT who was interested in perfecting a superior ostomy appliance. He coined the word "ostomate" by combining the suffix "ostomy" with the term for a person, "mate" (2). Until then, various other terms had been used, such as "stoma person," "ostomite," and even "person with an ostomy," but "ostomate" became and remained the standard term thereafter. An international Ostomy Association was established in 1975, principally because of the dedicated work of Vinitsky (4).

Norma Gill (5), under the aegis of the surgeon Dr. Rupert Turnbull in Cleveland, developed the concept of specifically trained professional therapists for ostomates. Thus, she was the first enterostomal therapist. At Mount Sinai, Marlene Brockmeier, and then Sally Bishop, both registered nurses, followed this pioneering work of Gill and Turnbull.

Ever since these pioneering efforts, the technical knowledge and advice for ostomates have been provided by enterostomal therapists, most of whom are nurses, some of whom have had stomas themselves. They have been specifically trained as professionals to teach, care for, and advise patients and doctors on the management of stomas. ETs (as they are usually referred to) often give instruction and advice at the ileostomy and colostomy meetings. Indeed, they themselves still learn from the ostomate groups. But the psychological and educational functions of the ostomy groups continue as before.

Perhaps the most important result achieved by these support groups has been their demonstration, by living example, that a person with a stoma can lead a healthy, happy life filled with all the joys and activities of "normal" people (1). In 1987, at a convention of enterostomal therapists, in response to a question on the continued usefulness and effectiveness of the ostomy groups, I characterized the need felt by ostomates for the ostomy societies as follows:

No land of birth nor right of name
Shall claim my family line,
But he and she who share my pain
Are brother, sister mine.

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To Make a Difference:

The Founding of the Crohn's and Colitis Foundation of America

SUZANNE ROSENTHAL

Abstract

In 1965, with the help of Dr. Henry D. Janowitz, Irwin M. Rosenthal established the Foundation for Research in Ileitis, Inc., now known as the Crohn's and Colitis Foundation of America, Inc. He was joined shortly thereafter by William D. Modell. At that time, the entire annual NIH budget for research on inflammatory bowel disease was only $25,000. Successful fund raising made it possible to recruit a research fellow at The Mount Sinai Hospital in the Division of Gastroenterology to study ileitis. Thereafter, the efforts of the foundation expanded nationwide. It supported a nationally coordinated research program and sponsored education for physicians, patients and the public. In addition, it established support groups to help patients and their families cope with Crohn's disease and ulcerative colitis. With the energy and philanthropy of the foundation's many lay leaders, tens of millions of dollars have been raised for research and education in inflammatory bowel disease.

Key Words: Ileitis, ulcerative colitis, colitis, regional enteritis, Crohn's disease, Crohn's and Colitis Foundation of America.

IN 1965 HENRY D. JANOWITZ, M.D. and Irwin M. Rosenthal took the first steps in creating what was to become the world's largest public, nonprofit inflammatory bowel disease (IBD) research, education and support organization: the Crohn's and Colitis Foundation of America, Inc. (CCFA). Each brought to their partnership a unique set of abilities and a deep commitment to the major goal of the foundation: to find the cause and cure for Crohn's disease and ulcerative colitis. Dr. Janowitz provided the expertise of a skilled clinician and scientist who, as chief of the Division of Gastroenterology of The Mount Sinai Hospital, had the authority to determine the direction of research and clinical care. Irwin Rosenthal, an attorney, provided the organization legal and leadership skills. The establishment of the foundation was completed shortly thereafter when Bill Modell, Chairman of the Board of the Modell's Sporting Goods chain, joined as a co-founder, providing the fund-raising, organizational and networking capabilities of one of the city's leading merchants.

Irwin was to remain president of the foundation for 10 years, and Henry, the founding chairman of the National Scientific Advisory Committee (NSAC) for 8 years. The third founding partner, Bill Modell, served as Chairman of the Board for 10 years. All three were critical to the financial success of the foundation as it grew over the years, changing its name from the Foundation for Research in Ileitis, to the National Foundation for Ileitis and Colitis (NFIC), and finally to the Crohn's and Colitis Foundation of America.

Henry D. Janowitz, MD, the physician member of this unique partnership, started his medical career at The Mount Sinai Hospital, concentrating on basic research in pancreatic inflammatory disease. In 1952, Dr. Janowitz moved into clinical medicine and, with the influence of Drs. Crohn and Ginzburg, together with the sheer number of IBD patients that he saw at Mount Sinai, was drawn into research on inflammatory bowel disease, publishing a number of important papers that advanced the knowledge of IBD clinical manifestations.

In 1958, Dr. Janowitz was asked by Dr. Alexander Gutman, the chief of Medicine at Mount Sinai, to form a division of gastroenterology. From the start, he knew that the division would have to engage physicians to combine classical practice with the intellectual rigor and academic curiosity of a laboratory scientist or clinical investigator. This philosophy prevailed, as he went on to train more than 125 fellows including Drs. Burton I. Korelitz, Daniel H. Present, Peter Banks, David Sachar, Lloyd Mayer, Jerome Waye, Lawrence Brandt, Eugene Strauss and dozens of others who, in time, would make their own contributions to the field. Dr. Janowitz's enthusiasm and expertise would soon play a major role in the founding of the Crohn's and Colitis Foundation of America.

In August 1956, Suzanne and Irwin Rosenthal were finally married — after several postponements because of Suzanne's painful and mysterious intestinal illness. Some three years later, the problem was diagnosed by Dr. Janowitz as ileitis. At that time, there were few

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medical and surgical treatments for this disease of unknown etiology.

Irwin, a young Yale Law School graduate and attorney with one of New York's leading corporate securities law firms, had been an activist in a number of civic and political organizations. So it was not unusual for him to challenge Dr. Janowitz, demanding of him a response to a question formed in the heat of his and Suzanne's deep frustration and anger, "Why doesn't someone do something about it?" Dr. Janowitz responded by challenging Irwin to fund a gastroenterology fellow to concentrate on ileitis research. It would cost at least $25,000 annually, which Dr. Janowitz informed Irwin was the amount of ileitis research then funded by the National Institutes of Health. Irwin accepted the challenge.

By early 1963, they were planning the establishment of an organizational effort to start "doing something about it." On December 17, 1965, the Foundation for Research in Ileitis, Inc. was officially incorporated in New York State, with Dr. Janowitz as its director of research and Irwin as its president. They now had the legal authorization to start raising money in New York State to support research. Together, they formulated the lay and medical partnership philosophy of the foundation; many of its principal medical research and research training concepts and programs are still in force today. They also determined that the NIH grant review system would be utilized to protect the quality of the research and the credibility of the foundation. All research monies, no matter where they came from, would flow into a single research fund, to be appropriated as determined by the grant reviewers and the Board of Trustees.

In January 1966, the very first meeting of the Board of Trustees of this new foundation was held at The Mount Sinai Hospital. The principles espoused by Dr. Janowitz and Irwin were unanimously approved. Irwin and Henry particularly had recruited Drs. Burrill Crohn, Leon Ginzburg and Gordon Oppenheimer, the three scientist-clinicians who discovered ileitis, as honorary co-chairmen of its scientific advisory board. Also recruited were Dr. Arthur H. Aufses, Jr., Suzanne's surgeon; Dr. Arthur Ludwig, her internist; Dr. Samuel K. Elster; Dr. Richard Marshak, the leading abdominal radiologist; and others who cared deeply about helping this young couple and Henry to find the cause and cure of ileitis. Friends and clients of Irwin's completed the lay portion of the foundation Board.

In 1966, with the foundation's legal basis in place, the research program officially began. Daniel H. Present, one of Henry's gastroenterology fellows, was recruited to organize a comprehensive research program, by compiling a list of existing and planned research projects. Mount Sinai gastroenterologists, surgeons, radiologists, nutritionists and immunologists were recruited to work either individually or jointly on a multidisciplined approach to "A Comprehensive Study of Regional Enteritis," including the effects of diet on motility, the mechanisms that cause kidney stones in ileitis patients, and the immunologic status of ileitis. The studies were conducted from 1966 to 1974, by Burton I. Korelitz, Robert Taub, Shelly Brown, Gerald Friedman and Charles Gerson, doctors then at Mount Sinai. One summer, a Mr. Barry Coller, then a medical student at New York University, was recruited to assist Dr. Present. Dr. Coller would later become the Murray M. Rosenberg Professor and chairman of the Department of Medicine at the Mount Sinai School of Medicine.

To conduct these studies, a small space in an unused apartment at 19 East 98th Street, provided by Mount Sinai, became the "research center." The bathtub was used to store pharmaceutical supplies, including those provided by Pharmacia, an early supporter of the foundation, to study the effects of Azulfidine suppositories on the treatment of proctitis. Beds for research patients were promised, and a group of patients was admitted to the Clinical Research Center, supported by a grant from the NIH. These patients were evaluated for various motility disturbances and symptomatology. Some patients remained under observation for as long as three weeks.

In 1966, with the Rosenthals' dining room table used as the foundation's "administrative office," Irwin began the fund-raising efforts which resulted in $25,000 for the first year's research. He accomplished this by letters of appeal concerning Suzanne's battle with ileitis. He sent them to family and friends, and to more than 1,000 members of his synagogue, with the blessing and permission of Rabbi Israel Mowshowitz. He urged them to help him raise funds to support ileitis research at Mount Sinai, and raised several thousand dollars. Each time Suzanne was hospitalized that year, and in future years, Irwin would prowl the halls of Mount Sinai to recruit the fathers, husbands and wives of other ileitis patients on the medical and surgical floors, to help raise money. Suzanne and Jane Present were recruited to prepare letters to send to Dr. Crohn's ileitis patients, asking for their assistance.

In the spring of 1966, Irwin asked Irving Rubin, from Detroit, Michigan, whose daughter was hospitalized at Mount Sinai, to help. Irving recruited his family and business associates, and he himself contributed funds for a very significant research effort. He was asked to underwrite an important conference with eminent gastroenterologists, on designing clinical trials, including a review of Drs. Present and Korelitz's proposed research protocol. Invited to attend were Dr. Joseph B. Kirsner of the University of Chicago, Dr. Fred Kern of the University of Denver, and Dr. Thomas Chalmers, a world renowned expert in the design of clinical trials. Dr. Chalmers, who was then serving at the NIH, would become the President/Dean of Mount Sinai in 1973.

While planning the research program of this new organization, Dr. Janowitz and his associates saw that clinical trials on the use of pharmaceuticals for ileitis were to be a major element. Dr. Daniel H. Present was awarded the first grant from the Foundation for Research in Ileitis, to prospectively study the pharmacological and therapeutic properties and side effects of 6-mercaptopurine (6-MP) in a controlled, double-blind study. Collaborators in the study included Drs. Burton I. Korelitz, David Sachar, and Nathaniel Wisch. The primary therapeutic effect to be studied was improvement of bowel function, fistulae and steroid sparing. There was careful monitoring of blood count to avoid marrow depression. The controlled trial ultimately took eight years to complete and was published in the *New England Journal of Medicine* in 1980 (N Engl J Med 1980; 302:981–987). An update on the history of drug treatment of inflammatory bowel disease can be found in Mt Sinai J Med 2000; 67:214–226.

This first Foundation for Research in Ileitis grant award and other Mount Sinai studies were to have an immense impact on today's scientific knowledge concerning inflammatory bowel disease. It was Burton I. Korelitz, one of Suzanne's original physicians at Mount Sinai, who had published a number of articles concerning ulcerative colitis (particularly with regard to the use of 6-MP in children and adults), who suggested to Irwin that the foundation include the study of ulcerative colitis in its research program. Dr. Janowitz concurred, and ulcerative colitis studies were added to the foundation's research portfolio. In 1967, the name of the foundation was changed to the National Foundation for Ileitis and Colitis (NFIC).

Bill Modell and his dynamic and talented wife, Shelby, joined the foundation efforts when their son Michael, then 14 years old, was diagnosed with ileitis by Dr. Burrill Crohn. They were referred to Irwin and Suzanne to learn how they could help find the cause and cure of the disease afflicting their son. With Michael as their inspiration, they provided the strong financial support for the foundation that was critical to its success, as well as to the progress of the ileitis and colitis research programs of the Division of Gastroenterology at Mount Sinai.

The Modells, experienced fund-raisers with strong business connections from their sporting goods stores in New York State, and with legions of caring family and friends, offered to chair the foundation's first major fund-raising event. In December 1967, a dinner dance at the glamorous nightclub of the Americana Hotel was arranged. With the Modells' huge and devoted following, Irwin and Suzanne's friends and clients, and members of the Board, the commitment to the hotel was met. The gala featured entertainment by Ella Fitzgerald, as well as a brief ceremony to honor Drs. Crohn, Ginzburg, and Oppenheimer.

Subsequently, with each passing year, with Shelby and Bill Modell as dinner chairpersons, the size of the banquet room increased to accommodate the burgeoning crowds of generous contributors. In addition to funds raised from the dinner, there were funds raised from journal ads for a journal book dedicated to the honorees. In the early years, Jane Present edited these successful journals. The list of honorees through the years has included people from the world of merchandising, politics, banking, government, medicine, pharmaceuticals and entertainment. The honorees also added to the excitement and glamour of the dinner dances, helping make them successful events. The net proceeds from the journal and the dinner, which came to be known as the Greater New York Chapter Annual Dinner, for many years contributed one-third of the national organization's gross revenue.

Today, the dinner, the largest single fund-raising event, still provides more than $1 million annually to the budget of the national foundation, now called the Crohn's and Colitis Foundation of America (CCFA). Bill Modell and Shelby co-chaired this dinner for 25 consecutive years until 1993, when they turned the dinner chairmanship over to their son Michael and his wife Abby, who continue in this role. Through the years, Shelby and Bill, and the Modell family have been responsible for raising more than $40 million for research and education. Bill Modell is still chairman of the Board, emeritus, and Shelby is national vice-president of the Board. They have been instrumental in the founding and development of the foundation's

Long Island chapter and the Gold Coast chapter of Boca Raton, Florida, contributing to the great financial success of each of these chapters.

Suzanne Rosenthal was the original inspiration for the founding of the CCFA and for Mount Sinai's intensified research efforts in the field of ileitis. She brought to the organization the management skills she learned at her college's business school and the wide knowledge she acquired about ileitis and colitis, and their treatment. These were of great value when she established the ladies auxiliary of the Board, with officers including Shelby Modell, Jane Present, Toby Fuchs, Dee Hollander and other women dedicated to building the foundation. Suzanne served as president and created committees for fund-raising, membership and patient education. Anticipating the growth of chapters, she wrote the operating manuals for chapter governance, membership, and education, as well as for chapter scientific advisory committees. Suzanne was well enough between hospitalizations to travel to many cities to help develop NFIC chapters along the East Coast, starting with the New York City boroughs and Long Island, then New Jersey, Westchester, Rhode Island, Boston, Philadelphia, Washington, D.C. and Greater Miami. In addition, Suzanne formed the government advocacy committee to help increase the NIH – National Institute for Diabetes, Digestive and Kidney Diseases' (NIDDK) inflammatory bowel disease research portfolio. Suzanne later became national president and remains chairman of the Board, emeritus.

In New York City, open education meetings for the public, with panels of ileitis and colitis medical experts (often Mount Sinai gastroenterologists), were held monthly. Upwards of one hundred patients and their families turned out for each meeting. In addition to the foundation's top priority of finding the cause and cure of inflammatory bowel diseases, patient and professional education became important goals. Eventually, mutual-help support groups would appear, first in New York City. This important program also became a major priority of the foundation.

During its first decade, the foundation was viewed as a Mount Sinai Hospital project, even though grants had been awarded to many researchers at other hospitals. In order to alter that perception, chairmanship of the National Scientific Advisory Board was to be rotated nationally among the leading IBD clinicians and scientists. NFIC President Irwin Rosenthal recruited Dr. Joseph B. Kirsner from the University of Chicago Medical Center as National Scientific Advisory Board chairman, and Dr. Kurt Isselbacher from Massachusetts General Hospital as Grant Review Committee chairman. He was to succeed Dr. Kirsner as NSAC chairman. Dr. Burton I. Korelitz, then chairman of Gastroenterology at Lenox Hill Hospital in New York, succeeded Dr. Isselbacher and formed subcommittees of the NSAC to address research training, professional education and patient education. He encouraged IBD clinical research investigators to participate more actively on committees, and organized conferences with research scientists and clinicians to exchange ideas. Word was widely circulated that funds were available to investigators from all over the United States and abroad.

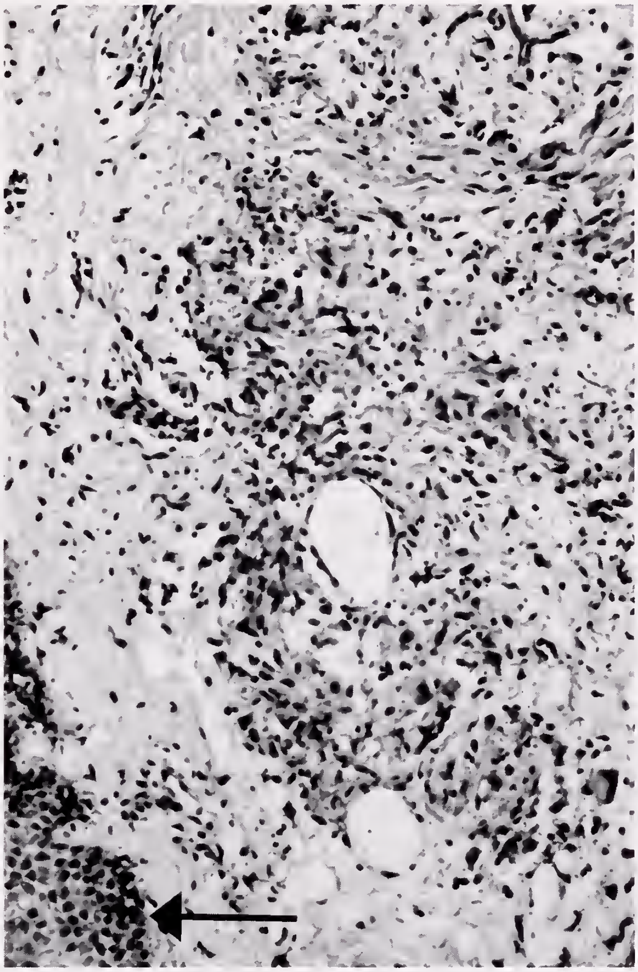
Today, the CCFA has a large suite of offices at 386 Park Avenue South at 27th Street in New York City, to appropriately service an organization with a $21 million budget. The CCFA has 60,000 lay and physician members. Its 55 chapters across the country offer more than 350 support groups. It has published four books for patients and distributes annually more than one million educational IBD brochures, newsletters, etc. CCFA publishes *Inflammatory Bowel Disease*, its own medical journal, which is now listed in the Index Medicus. The CCFA is a partner with the NIH in research conferences and workshops that significantly advance IBD research. Through its strong Congressional advocacy efforts, it has helped two NIH institutes to progressively expand their funding for IBD research portfolios. Today, the NIDDK funds more than $21 million in IBD research grants. The National Institute for Allergy and Infectious Diseases (NIAID) funds close to $3 million for IBD immunology research.

More than 75% of the research investigators funded by the NIH in the last five years were first funded with CCFA seed money to help them develop and refine their projects. This was the vision of its founders. Irwin and William remain active with the foundation to this day. The CCFA continues to provide seed money for the development of IBD research to enable investigators to compete more successfully for the highly competitive NIH grant awards that provide considerably more funds for research projects.

As CCFA enters a new millennium in which many questions about IBD remain to be answered, clinicians and scientists at Mount Sinai and around the world are increasingly more hopeful that the cause and cure of these diseases will be found within the next decade. When this happens, CCFA members will know that they have played an important part in this success — that they have made a difference.

Dermatology Notes

Metastatic Crohn's Disease



METASTATIC CROHN'S DISEASE is characterized by noncaseating granulomas in skin lesions that are remote from the gastrointestinal tract. The arrow marks the epidermis. (Hematoxylin and eosin-100X)

—Robert Phelps, M.D., and Mark G. Lebwohl, M.D.

Abstracts

*The following abstracts were presented by investigators at the Eighteenth Annual Samuel Bronfman Department of Medicine Research Day on October 24, 2000 at the Mount Sinai Medical Center. Most of the investigators serve in the Samuel Bronfman Department of Medicine, including those working at affiliated institutions such as The Bronx Veterans Affairs Medical Center, Bronx, NY; Elmhurst Hospital Center, Elmhurst, NY; Queens Hospital Center, Jamaica, NY; and St. Joseph's Hospital and Medical Center, Paterson, NJ. The work outlined in four abstracts, only two of which have been identified in this publication with an *, were presented in the morning plenary session. These two, and several additional abstracts (posters) shown on Research Day, have been published elsewhere. Abstracts from Queens Hospital Center were presented as posters on Research Day held at that institution.*

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Research in Medicine 2000
Mount Sinai School of Medicine

Alcohol Research

Combined Effects of Acetaldehyde and β-Carotene on Oxidative Status and Glutathione Metabolism in HepG2 Cells. Ruoyu Ni, Leo MA, Hu C, and Lieber CS. Alcohol Research and Treatment Center, Section of Liver Disease and Nutrition, Bronx VA Medical Center and Mount Sinai School of Medicine, New York, NY.

Background: We previously showed that β-carotene potentiates the hepatotoxicity of ethanol. Since much of ethanol's toxicity is due to acetaldehyde, we investigated the effects of acetaldehyde combined with β-carotene on oxidative status and glutathione metabolism in liver cells *in vitro*.

Methods: A human liver tumor cell line, HepG2 cells, was treated with acetaldehyde and/or β-carotene. Reactive oxygen species (ROS) production was detected with the fluorescent probe DCF-DA; glutathione levels were measured with a kit from Cayman Chemical; glutathione peroxidase (GPx) and glutathione reductase (GR) activities were measured with kits from OXIS International, Inc.; and the mRNA steady-state levels of γ-glutamylcysteine synthetase (GCS), the rate limiting enzyme of glutathione synthesis, were determined with Northern blotting.

Results: Acetaldehyde increased ROS production and decreased reduced glutathione (GSH) levels after acute exposure. However, 24 hours later, total glutathione, GSH and oxidized glutathione (GSSG) rose significantly ($p<0.001$, $n=12$). mRNA steady-state levels of light (GCSl) and heavy (GCSh) chain subunits of GCS rose 3.1 and 5.5 fold respectively ($p<0.001$, $n=4$), and these effects were dose and time dependent. An increase in glutathione peroxidase (GPx) activity was also observed ($p<0.01$, $n=6$). These changes most likely represent an adaptive response to the acetaldehyde induced oxidative stress. β-carotene alone increased both ROS and GSH compared to reagent controls, but in concentrations of >10 μM, an inhibiting effect was observed in ROS production. When it was combined with acetaldehyde, additive effects were evident. Total glutathione and GSSG increased further ($p<0.05$, $n=12$); GCSl mRNA rose with increasing β-carotene concentrations (0–24μM).

In conclusion, acetaldehyde increases oxidative stress and causes an adaptive response of glutathione metabolism in HepG2 cells. The mechanism of the glutathione increase appears to be *de novo* synthesis, as indicated by increases of both the total glutathione and the mRNA steady-state levels of GCS. These were exacerbated by the addition of β-carotene, which may act as a pro-oxidant, and this may thus explain the hepatotoxic ethanol-β-carotene interactions *in vivo*.

Polyenylphosphatidylcholine (PPC) Opposes Alcohol-Induced Oxidative Stress and Hepatic Fibrosis in Man: Preliminary Results. C.S. Lieber, M.A. Leo, S. Aleynik, N. Lowe, M. Aleynik, and F. Paronetto. Alcohol Research Center, Bronx VA and Mount Sinai Medical Centers, New York, NY.

Alcohol is preferentially metabolized in the liver and the associated oxidative stress is a major cause of liver injury. In both rodents and non-human primates, PPC effectively opposed this oxidative stress. To determine whether it has a similar action in humans, 18 volunteers with a history of heavy alcohol consumption (associated with significant liver injury, including some fibrosis but no complete cirrhosis) were studied. They were given randomly for 2 years 3 tablets daily of either 1.5 gram PPC or placebo, donated by Rhone-Poulenc Rorer & Co. (Cologne, Germany). Their compliance, assessed by clinic attendance, exceeded 90% and by pill consumption 80%. Compliance was also corroborated in those taking PPC by a significant ($p=0.01$) increase in the blood concentration of the 2 main phosphatidylcholine (PC) species of PPC, namely dilinoleoyl PC and palmitoyl-linoleoyl PC (measured by HPLC). These two species comprise 40–52 and 23–24% (respectively) of all PCs in PPC. There was no significant difference in alcohol consumption between the 2 groups, but PPC did strikingly affect 3 standard plasma markers of oxidative stress: In PPC vs placebo, they were, respectively, malondialdehyde (measured according to Rauli et al. 1998) 7.6 ± 0.9 vs 15.7 ± 3.9 ng/ml ($p=0.04$), free F2-isoprostanes (measured by GC-MS) 20.7 ± 3.0 vs 41.4 ± 7.8 pg/ml ($p=0.02$) and Total Peroxyl Radical-Trapping Potential (TRAP) measured according to Valkonen & Kuusi (1997) 18.9 ± 1.0 vs 15.9 ± 0.4 min. ($p=0.006$). Liver fibrosis, assessed both by a standard method (Worner and Lieber, 1985) and by semi-quantitative analysis (Chevalier et al., 1994), showed progression in 5 of 9 placebo-treated and no change or regression in the 9 subjects given PPC ($p<0.02$).

Conclusions: Therapeutic effects of PPC demonstrated experimentally, namely its antioxidant and antifibrotic actions, were confirmed in this preliminary randomized, double-blind placebo-controlled human trial. This is now being verified in a much larger multicenter study.

Supported, in part, by NIH (NIAAA) grant AA09479.

Cytokeratin 7 Staining of Hepatocytes Predicts Progression to More Severe Fibrosis in Alcohol-Fed Baboons. Chaolin Ren, Fiorenzo Paronetto, Ki M. Mak, M.A. Leo, and C.S. Lieber. Alcohol Research Center, Bronx, NY, Department Pathology and Laboratory Medicine, VAMC Bronx, NY.

It has been reported that not all alcoholic patients develop progressive liver disease. Thus, it would be important to determine whether some markers could predict progression of liver fibrosis. To that effect we have used a baboon model that closely mimics human alcoholic liver disease, and we measured cytokeratin 7 and 19. In normal liver, cytokeratin 7 is restricted to bile duct cells, but staining of hepatocytes (called ductular metaplasia of hepatocytes) has been previously described in human alcoholic and cholestatic liver disease.

Cytokeratin 7 and 19 were investigated in formalin-fixed, paraffin-embedded liver biopsies taken serially in 18 animals undergoing prolonged alcohol administration (range 2 to 17 years) and in 4 controls. Animals were pair-fed a liquid diet in which carbohydrate (50% of calories) had been replaced isocalorically with ethanol. Cytokeratin 7-positive hepatic and ductular cells were counted and expressed as number per field. Fibrosis was graded as follows: 0 no fibrosis; 1 perivenular fibrosis; 2 septal fibrosis; 3 incomplete cirrhosis; 4 complete cirrhosis. Fibrosis was also quantitatively assessed by computer-assisted image analysis and expressed as percentage of Sirius red-stained area to the total area measured.

Eight animals fed alcohol exhibited a progression of liver disease from no fibrosis or perivenular fibrosis to septal fibrosis or cirrhosis within 7 years. Ten animals did not show a progression of liver disease even after 17 years of alcohol administration. Of the markers investigated, only hepatocellular cytokeratin 7 predicted the progression of liver disease from no fibrosis or perivenular fibrosis to septal fibrosis. Hepatocyte cytokeratin 7 anticipated the subsequent progression of liver disease on the average by four years. However, there was no correlation between the number of cytokeratin 7-positive hepatocytes and the extent of fibrosis measured either by image analysis or histological score, but there was a good correlation ($r=0.77$; $p<0.0001$) between image analysis and histological grading of fibrosis.

Our study indicates that in alcohol-fed baboons cytokeratin 7 staining of hepatocytes predicts future progression to more severe liver disease. Clinical studies are now warranted.

Effects of Alcohol and Polyenylphosphatidylcholine on Hepatic Nitric Oxide Production and Its Peroxynitrite-Mediated Toxicity. E. Baraona, G. Zeballos, I. Kessova, K. Mak, and C.S. Lieber. Section of Liver Disease and Nutrition, Alcohol Research Center, Bronx VA and Mount Sinai Medical Center, New York, NY.

Background: Nitric oxide (NO) is a physiological mediator which may become deleterious when its production is associated with enhanced superoxide (O_2^-) formation, leading to the synthesis of peroxynitrite, which nitrosates biologically important proteins. Polyenyl-phosphatidylcholine (PPC), a 95% pure polyunsaturated phosphatidylcholine extract from soybeans, decreases alcohol-induced liver injury, an effect attributed in part to its antioxidant properties. The interaction between PPC, alcohol and NO metabolism is unknown.

Methods: To study this, 24 rats were pair-fed diets containing 36% of energy either as ethanol or as additional carbohydrate for 24 days and sacrificed 90 min after intragastric feeding. Half received PPC in the diet and the other half equivalent amounts of unsaturated fatty acids and choline. NO was measured by chemiluminescence in arterial blood, in liver and as a product of the inducible NO synthase activity (iNOS). Peroxynitrite formation was assessed by the increase in nitrotyrosine protein residues (NTP).

Results: In blood, alcohol doubled the concentration of NO. This was unaffected by PPC. In the liver, alcohol increased NO by 57% ($p<0.01$), an effect attenuated (43%; n.s.) by PPC. Whereas control rats had very low iNOS activity in the liver, alcohol consumption increased the cytosolic activity 5-fold and engendered NO synthetic activity in microsomes normally devoid of this activity. The latter could be due to NO production by alcohol-induced CYP 2E1. PPC decreased the ethanol effect on both the cytosolic and the microsomal activities. Immunohistochemically, the changes in iNOS activity were observed diffusely in the hepatocytes. The alcohol-enhanced NO production was associated with an 18% ($p<0.01$) increase in NTP, products of peroxynitrite. Increased NTP immunostaining was seen mainly in steatotic hepatocytes.

Conclusions: (1) Ethanol increased circulating NO (mainly a product of endothelial NO synthase); this was not affected by PPC. (2) In the liver, alcohol feeding increased peroxynitrite toxicity by enhancing concomitant production of NO and O_2^-, effects which were prevented by supplementation with PPC, shown to act as an antioxidant.

Attenuation of TNF-α Generation by Dilinoleoylphosphatidylcholine (DLPC) Correlates with CYP-2E1 Expression in Ethanol-Fed Rat Kupffer Cells Treated with Acetaldehyde (ACH) but not Lipopolysaccharide (LPS). Q. Cao, K.M. Mak, and C.S. Lieber. Alcohol Research Center and Section of Liver Disease, Bronx VAMC and Mount Sinai School of Medicine, New York, NY.

Chronic ethanol feeding upregulates CYP2E1(2E1) expression in rat Kupffer cells, but it is not known if this induction plays a role in the generation of the cytokine TNF- , which mediates early alcoholic liver injury. DLPC, the main phosphatidylcholine species of polyenylphosphatidylcholine (PPC) extracted from soybeans, decreases TNF- production in LPS-activated Kupffer cells. This study was conducted to determine if TNF- generation in Kupffer cells stimulated by ACH or LPS is associated with 2E1 induction by ethanol and whether DLPC opposes this through 2E1 downregulation. Kupffer cells, isolated from rats fed Lieber-DeCarli alcohol-containing or control diets for 3 weeks, were cultured in serum-free medium containing: 1) .05% bovine albumin (control), 2) 10 µM DLPC, 3) 200 µM ACH, 4) 200 µM ACH + 10 µM DLPC, 5) 10 µg/ml LPS, 6) 10 µg/ml LPS+10 µM DLPC. After 4 – 24 hr, the S9 protein was isolated for 2E1 content by Western blot and of its catalytic activity by hydroxylation of p-nitrophenol. Culture media were assayed for TNF- concentrations by ELISA. Ethanol feeding caused a 9-fold rise in 2E1 content in Kupffer cells ($p<0.001$), with a 6-fold rise in its catalytic activity ($p<0.001$). The corresponding increases were 7- and 5-fold after 4 hr culture. ACH treatment for 4 hr in cells of ethanol-fed rats enhanced TNF- production 4.7-fold, with a concomitant rise in 2E1 content (15±0.6%, $p<0.05$) and in catalytic activity (48.4±4.5%, $p<0.05$). LPS also increased TNF- (3.5-fold), but it had no effect on 2E1 expression. TNF- production correlated with 2E1 activities in ACH-treated cells ($p<0.05$). DLPC decreased ACH-mediated TNF- production by 37.5% ($p<0.05$), and LPS-mediated TNF- production by 24.0% ($p<0.05$). The decrease in TNF- production by DLPC correlated with a decrease in 2E1 catalytic activity in ACH ($p<0.05$) but not in LPS-treated cells.

Conclusions: Chronic ethanol feeding increases 2E1 that sensitizes Kupffer cells to the stimulatory effects of ACH or LPS on TNF- production; DLPC treatment opposes this effect and thus might be useful for the treatment of alcoholic liver disorders.

Prevention of TGF-β1-mediated Collagen Accumulation by Dilinoleoylphosphatidylcholine (DLPC) Is Mediated by MMP-13 Activity in Rat HSC Culture. Q Cao, KM Mak, and CS Lieber. Alcohol Research Center and Section of Liver Disease, Bronx VAMC and Mount Sinai School of Medicine, New York, NY.

Polyenylphosphatidylcholine (PPC), a mixture of polyunsaturated phosphatidylcholines (PC) extracted from soybeans, protects against alcoholic fibrosis and cirrhosis in baboons and CCl_4-induced fibrosis in rats. PC decreases the acetaldehyde-induced collagen accumulation in HSC cultures, and this effect is due, in part, to the stimulation of collagenase by DLPC, the main species of PC. TGF-β1 is a profibrogenic cytokine and its production is commonly increased in alcoholic liver disease. Furthermore, TGF-β1 has been implicated to play a role in the acetaldehyde-induced α(1) I procollagen gene expression. Therefore, this study was conducted to determine whether DLPC prevents TGF-β1-mediated collagen production in rat HSCs. To that effect, HSCs were treated with 2 ml of serum-free medium containing: (1) 0.05% bovine albumin (as control); (2) 8 ng/ml TGF-β1; (3) 10 μM DLPC; or (4) DLPC and TGF-β1. After 24 hr, collagen type 1 and TIMP-1 concentrations, and MMP-13 activity in culture media were assayed and total RNA from HSCs were isolated for Northern blot analysis of α(1) I procollagen and TIMP-1 mRNA expression. TGF-β1 increased collagen type I and TIMP-1 accumulation in the media by 67% (vs control, $p<0.001$) and 141% (vs control, $p<0.001$), respectively, while it decreased the activity of MMP-13 in the media by 73% (vs control, $p<0.001$). TGF-β1 also increased the levels of mRNA expression of α(1) I procollagen by 57% (vs control, $p<0.001$) and that of TIMP-1 by 54% (vs control, $p<0.001$). DLPC, in the presence of TGF-β1, blocked the cytokine-induced collagen type I ($p<0.001$) and TIMP-1 ($p<0.01$) accumulation in the media, whereas it partially reversed the TGF-β1-induced decreased MMP-13 activity ($p<0.01$). DLPC, in the presence of TGF-β1, prevented the cytokine-induced increased mRNA expression of α(1) I procollagen and of TIMP-1.

Conclusions: DLPC prevents the TGF-β1-mediated increase of collagen type I production by activated HSCs, and this is attributable to a downregulation of α(1) I procollagen and TIMP-1 mRNA expression; the latter effect leads to a decrease in TIMP-1 production, resulting in an increase in MMP-13 activity and, hence, a decrease in collagen accumulation. This effect of DLPC may explain, at least in part, the antifibrogenic action of PPC which may be beneficial not only against alcoholic but also against other fibrotic disorders.

Cardiology

National Versus Local Performance Indicators for Quality Improvement in Myocardial Infarction Care. I.S. Nash[1,2], M. McLaughlin[1,2,3,4] and A. Siu[2]. [1]Zena and Michael A. Wiener Cardiovascular Institute, [2]Department of Medicine, [3]Department of Geriatrics, [4]Department of Health Policy, all of the Mount Sinai School of Medicine, New York, NY

The Cooperative Cardiovascular Project (CCP) developed quality indicators for myocardial infarction (MI) care based on guidelines prepared jointly by the American College of Cardiology and the American Heart Association. Feedback on the quality of MI care to individual institutions was based on a small number of "ideal" candidates for specific therapies. We sought to evaluate local MI care more extensively. Evidence-based treatment guidelines were developed for aspirin (ASA), B-blockers (BB), ACE inhibitors and reperfusion strategies and the non-use of calcium antagonists. Trained abstractors retrospectively reviewed charts of patients discharged from The Mount Sinai Hospital (NY) with a principal diagnosis of MI between Jan 96 and Oct 97. Appropriate candidates were defined as those with indications and no contraindications. We compared the percent of our patients identified as appropriate (A) with the percent identified as ideal (I) by the CCP (Marciniak, JAMA 1998;279:1351-7) and the percent of those groups actually treated, for ASA and BB on discharge. 523 MI patients were identified. All admissions and a random sample of transfers were abstracted (317) and 293 patients were alive at discharge.

	CCP (N=6142)		Mount Sinai (N=293)		P value
	% Ideal	% Rx	% Appropriate	% Rx	I vs A
ASA	57.2	85.2	95.2	97.8	<0.0001
BB	20.8	65.7	60.4	94.9	<0.0001

Conclusion: Less restrictive definitions of eligibility for these drugs than those used by the CCP are practical. Such broad eligibility criteria may facilitate wider use of effective treatments in MI, as well as more meaningful assessments of the quality of care. GCO# 96-244HP

P Wave Morphology with Pulmonary Vein Pacing. D. Mehta[1], J.A. Gomes[1], N. Langan[1], and M.E. Hoffman[2]. [1]Division of Electrophysiology, Department of Cardiology, Mount Sinai Medical Center, New York, NY, and [2]Mount Sinai School of Medicine, New York, NY.

A significant proportion of focal atrial fibrillation originates in the pulmonary veins (PV). Mapping of atrial premature beats is used to identify these sights for ablative purposes. In order to identify the P wave morphology of atrial premature beats originating from the 4 PV's, 12-lead ECG's were performed while pacing the ostia of all 4 PV's.

Methods: Nine patients undergoing trans-septal punctures for ablation of the left-sided accessory pathways were prospectively studied. Following the ablation procedure, a pacing catheter was advanced into all 4 PV's. While pacing at 100–110 bpm, the catheter was withdrawn until atrial capture was obtained. Twelve lead ECG's were continuously performed while pacing. Resulting P waves in all 12 leads were identified as predominantly positive or negative.

Results: Significant differences were seen between the ECG's taken while pacing the left and right PV's. Left PV pacing (upper and lower) resulted in positive P waves in lead aVR ($p<0.05$), and negative P waves in aVL ($p<0.001$). Additionally, left lower PV pacing resulted in negative P waves in leads V3 ($p<0.001$), V4 ($p<0.05$), V5 ($p<0.05$), V6 ($p<0.05$). Right PV (upper and lower) pacing, resulted in negative P waves in lead aVR and positive P waves in lead aVL. There were no significant differences in morphology when pacing right upper or lower PV's when compared to the P waves produced by normal sinus rhythm.

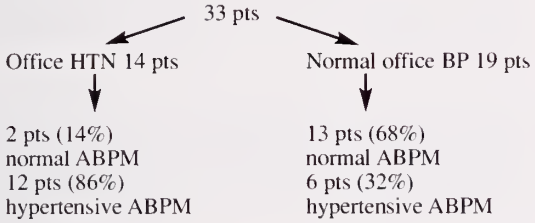
Conclusions: (1) The morphology of P waves in leads aVR and aVL can be used to differentiate between foci originating from the right and left PV's. (2) The morphology of P waves in precordial leads V3–V6 can be used to differentiate between foci originating from left upper and lower PV's. (3) There are no significant differences in the P wave morphology between foci originating from the 2 right PV's. Thus, 12-lead ECG is useful in determining which pulmonary vein is the origin of atrial premature beats. Localization of abnormal impulses may aid in therapy of focal atrial fibrillation.

Screening for Hypertension in Kidney Donors: Office or Ambulatory 24-Hour Blood Pressure Measurements? Alexander Butkevich, MD, Barbara Murphy, MD, Arlene Travis, RN, and Robert A. Phillips, MD, PhD. Mount Sinai School of Medicine, New York, NY.

Background: Hypertension in kidney donors may be associated with greater risk of increase in BP after unilateral nephrectomy. Ambulatory 24-hour blood pressure monitoring (ABPM) is a more accurate tool for diagnosing hypertension than office BP measurements, but its role in screening of potential kidney donors for hypertension is not established.

Methods: We compared clinic BP measurements with the results of ABPM in 33 (19 F and 14 M) potential kidney donors, who were hypertensive in the clinic and referred for ABPM to our institution.

Results. The mean (±SD) age of the subjects was 46.8±13 years, and BMI was 28.7±4.3 kg/m^2. Overall, hypertension was confirmed by ABPM in 12 out of 33 potential kidney donors (36%) who were hypertensive in the clinic. Moreover, 57% of these patients were normotensive by our office measurements. Our office BP measurements led to misclassification of 8 patients (24%) as hypertensive (2/14 patients) or normotensive (6/19 patients).



Conclusions and Implications: Office BP measurements were inaccurate and not reproducible in screening for hypertension in this selected, healthy, middle-aged, overweight population. Ambulatory BP monitoring may be warranted for screening for hypertension in kidney donors. Use of ABPM might increase the donor pool for kidney transplant.

Amlodipine vs Losartan in the Treatment of Mild to Moderately Severe Hypertension. R. Phillips, M.D., R.A. Kloner, M.D., Weinberger, M.D., and R.H. Grimm, M.D., Ph.D. Mount Sinai School of Medicine, Indiana University and the University of Minnesota.

A multicenter, randomized, double-blind, placebo-controlled trial was conducted to assess antihypertensive efficacy of once-daily amlodipine versus losartan in adults (age range 45 – 80 years) with mild to moderately severe essential hypertension. After a 2-week single-blind placebo run-in period to obtain baseline values, patients were randomly assigned to double-blind treatment with either amlodipine (n=218) or losartan (n=222). During the following 12-week Titration Phase, patients received a fixed dose for the first 6 weeks. For the second 6 weeks, patients who failed to meet the BP goal of reduction of average sitting diastolic blood pressure (ASDBP) to less than 90 mm Hg could have their dose titrated from amlodipine 5 mg to amlodipine 10 mg or from losartan 50 mg to losartan 50 mg+HCTZ 12.5 mg. After the Titration Phase, patients entered the 4-week Maintenance Phase at their optimal dose.

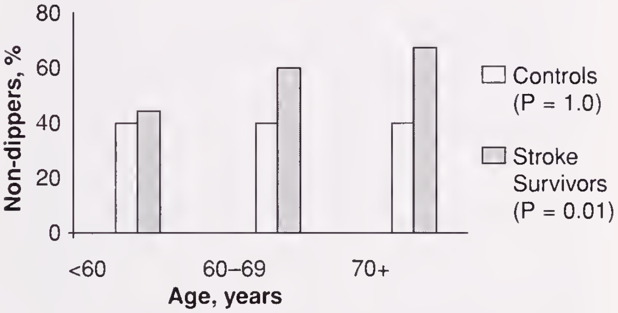
For the primary endpoint of number of patients to reach ASDBP reduction goal, there was a trend of a greater percentage of patients in the amlodipine group compared to the losartan group attaining the goal BP at the end of titration (amlodipine: 69%; losartan: 61%, p=0.085) and at the end of maintenance (amlodipine: 64%; losartan: 55%, p=0.070). In the amlodipine group, 61% of the patients entered maintenance after dose titration to 10 mg and in the losartan group, 66% of the patients entered maintenance after dose titration to losartan 50 mg+HCTZ. At the last maintenance visit of this dose-adjusted subgroup, 59% of the amlodipine-treated patients vs. 42% of the losartan-treated patients met BP goal. This difference in treatment groups was significant (p=0.009). Amlodipine was also more efficacious than losartan in the black subgroup at the end maintenance (62.5% of amlodipine-treated patients met BP goal, compared to 41.4% of losartan-treated patients, p=0.033). The least-squares adjusted mean reduction in ASDBP from baseline to the last treatment visit (mmHg) was statistically significantly greater in the amlodipine group than in the losartan group (amlodipine: baseline=100.27, endpoint=87.63; losartan: baseline=99.73, endpoint=89.44, p=0.002). In both treatment groups there was significant and equivalent reduction of 24 hour blood pressure measured with ambulatory BP monitoring. The results of this study support the antihypertensive efficacy and safety of amlodipine and losartan for the treatment of mild to moderately severe essential hypertension in adults.

Age Increases the Risk of Stroke Associated with Non-dipping. Robert A. Phillips, MD, PhD, Kara Sheinart, MD, Alexander Butkevich, MD, James Godbold, PhD, and Stanley Tuhrim, MD. Mount Sinai School of Medicine, New York, NY.

Introduction: Blood pressure in most individuals exhibits a characteristic nocturnal decline or dipping. Hypertensive subjects with a blunted or absent nocturnal BP dip (non-dippers) have a greater risk of cardiovascular events than dippers with a similar daytime BP. We evaluated the association of non-dipping, age and stroke in a case-control stroke study.

Methods: 217 control subjects and 166 stroke survivors enrolled in the Minority and Risk Factors for Stroke Study (MRFASS) underwent 24-hour ambulatory BP monitoring. Non-dipping was defined as a decrease of less than 10% in sleeping systolic or diastolic BP relative to waking levels. Multiple regression analysis was used to assess the association between non-dipping, age and the risk of stroke.

Results: There were significantly more non-dippers in stroke survivors than in control subjects. Non-dipping was significantly related to age in stroke survivors (gray bars), but not in controls (open bars).



Conclusions: Non-dipping is more common in stroke survivors aged 60 and higher than in control subjects of similar age. This may reflect an increased fragility of blood vessels and susceptibility to stroke in older subjects whose blood pressure fails to dip during sleep.

Reversible Low Voltage ECG Produced by Marked Peripheral Edema: Description of a New ECG Syndrome. Moethu Win, Himanshu Agarwal, Raveen Bazaz, Lalitha Medepalli, and John E. Madias. Mount Sinai School of Medicine, New York University, and Elmhurst Hospital Center, New York, NY.

We have studied 28 patients (pts), 10 men, aged 70.4±14.9, (mean±SD), among 493 consecutive pts admitted in our CCU who developed progressively reduced amplitude of their ECG in the context of gaining weight (wt). The pts were in need of vasopressor drugs, and large quantities of fluids for hypotension; also they were receiving respiratory ventilation via an endotracheal tube. The pts were treated for aspiration pneumonia, sepsis, status post cardiac arrest, and ARDS. Although the patients' clinical course revealed many clinical, hemodynamic, and laboratory alterations, with occasional long intervals of improvement in their condition, they all gradually gained wt (48.9±28.1) lbs, despite careful management of their illness, and intensive high-protein feeding by the intravenous and gastrointestinal routes. Echocardiograms and chest x-rays excluded pericardial effusions and pneumothoraces. Myocardial infarction was ruled out. Admission (Ad) wt was 148.9±37.8 lbs, and peak (Pk) wt was 197.8±52.3 lbs, (p=0.0005), while the corresponding sums of the total amplitude (highest positive + lowest negative) of the QRS complexes of the 12 ECG leads (SQRS) in mm, measured in each lead to the nearest 0.5 mm, were 120.2±41.6 mm on Ad, and 54.8±26.9 mm at the time of Pk wt, (p=0.0005). Correlation of wt gain, and attenuation of SQRS, corrected for Ad values of these 2 variables, revealed an R=–0.61, and a p=0.001. Thus, marked peripheral edema results in attenuation of the ECG transfer resistance, leading to "short-circuiting" and resultant decrease of the amplitude of the ECG complexes. This is a result of the decrease in the peripheral resistance from the accumulation of peripheral edema fluid, which is known to have the lowest resistivity (special resistance) in biological systems. Consequently, and as per Ohm's law (V=I x R, V=potential, I=current, R=resistance) the surface ECG potentials gradually decrease, as accumulation of peripheral edema progresses.

High Prevalence of Left Ventricular Hypertrophy and Diastolic Dysfunction in Inner-city African-Americans with Congestive Heart Failure. M.A. Rafey, A. Kassim, and M. Maw. Department of Medicine, North General Hospital.

Congestive heart failure (CHF) is a disease with a high morbidity and mortality, and a leading cause for hospitalization in the elderly. Data on African-American patients is limited, as they have been under-represented in major trials done on CHF (1). The available data has suggested that this segment of population has a higher prevalence of diastolic dysfunction when compared to whites.

Purpose: To study the prevalence of left ventricular dysfunction and left ventricular hypertrophy (LVH) in African-American inpatients with CHF, at an inner-city hospital.

Methods: Seventy African American patients admitted to North General Hospital with a primary diagnosis of CHF (International Classification of Diseases-9) over a 6-month period were studied retrospectively.

Patients with a non-cardiac cause for dyspnea were excluded. M – mode echocardiography was used to determine left ventricular wall measurements and ejection fraction.

Left ventricular mass (in grams) was estimated using the formula of Devereux and Reichek (LV mass in grams = 1.04 [(LVID + VST +PWT)3 – (LVID)3] – 13.6 (2). Applying the correction for left ventricular mass by height (LV mass in grams/ height in meters), sex-specific cutoff values of 143 g/m for men and102 g/m for women were used to define LVH (3).

61% of the study patients were women. The mean age of women was 75 (±12) years and that of men was 68 (±12) years. All patients satisfied the Framingham criteria for CHF.

Results: Normal systolic function (left ventricular ejection fraction > 0.45) was found in 48.6% of patients (48.1% of men, 48.8% of women; p value = 1.00). LVH was found in 84.6% of patients (73% in males and 92% in women, with a p value of 0.075).

TABLE

	Overall	Men (n=27)	Women (n=43)	p value
Age in years Mean (SD)	74.7 (13)	68 (12)	75 (12)	0.02
LV Ejection Fraction < 0.45	36 (51.4%)	14 (51.9%)	22 (51.2%)	ns
LVH (n=65)	55 (84.6%)	19 (73.1%)	36 (92.3%)	ns

Conclusions: The prevalence of diastolic dysfunction found in this study was higher than that reported in earlier studies. The mean age of the patients studied was 74.7 (±13) years and 90% of the patients were severely decompensated (37.5% and 52.5% in New York Heart Association classes III and IV respectively). LVH was found in a high proportion of patients. This may be attributed to the high prevalence of hypertension in African-American patients which leads to left ventricular muscular hypertrophy and consequent left ventricular diastolic dysfunction.

LVH is a major prognostic factor in CHF (4). The high prevalence found in this study indicates a need for more stringent control of hypertension in this subset of patients, as both the prognosis and management of CHF with diastolic dysfunction differ from systolic dysfunction. Early screening for LVH by echocardiography in African-Americans with longstanding hypertension would be needed to optimize treatment protocols and thereby limit morbidity and mortality.

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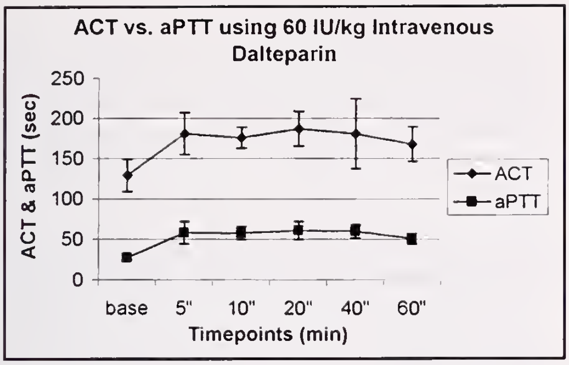
Activated Clotting Time (ACT) Can Be Used to Predictably Monitor the Anticoagulant Effect of Dalteparin (Fragmin) during Percutaneous Coronary Intervention (PCI). M.F. Richard, R.S. Bagga, S. Anand, J.J. Badimon, S.K. Sharma, and J.D. Marmur.

Background: Low molecular weight heparins (LMWH) may become the treatment of choice in PCI. Advantages of LMWH over unfractionated heparin include a more reliable bioavailability and a decreased incidence of thrombocytopenia. However, their use in the cardiac catheterization laboratory may be limited by the inability to monitor their anti-thrombotic effect. The ACT is the most widely used assay to assess the degree of anticoagulation during PCI. The objective of this study was to determine whether the ACT could be used to monitor the anticoagulant effect of dalteparin during PCI.

Materials and Methods: Ten patients scheduled for PCI were administered dalteparin intravenously 60 international units (IU)/ kg followed by an infusion 10 minutes later of abciximab. We measured ACT, aPTT (activated partial thromboplastin time), Xa activity, and the whole blood clot signature analyzer by Xylum Inc. to assess the anticoagulant effect. Measurements were taken at baseline, 5, 10, 20, 40, and 60 minutes after dalteparin administration.

Results: After dalteparin administration the ACT increased from 130±17 to 181±27 at 5 minutes post infusion of dalteparin. This increase was sustained for 40 minutes and was associated with a corresponding increase in aPTT values. APTT values correlated to the ACT (r=0.97). An ACT of 175 was consistently associated with a therapeutic aPTT > 60 sec. and Xa levels of 40–50% below baseline.

Conclusions: Our data suggest that the ACT may be used to monitor the anticoagulant effect of dalteparin. The ability to monitor dalteparin may facilitate the use of LMWH in the cardiac catheterization laboratory. These preliminary observations suggest an ACT of 175 sec as a therapeutic target in dalteparin-treated patients.



Severity of Atherosclerotic Lesions in ApoE-/- Mice Assessed by Non-invasive *In Vivo* High Resolution Magnetic Resonance Microscopy.

J. Gilberto Aguinaldo, Robin P. Choudhury, James X. Rong, Chrystie Yodice, Amy Kulak, Jessica Kulak, John T. Fallon, Edward A. Fisher, Valentin Fuster, and Zahi A. Fayad.

The apolipoprotein E-deficient (ApoE-/-) mouse is a standard animal model of human atherosclerosis. We have previously shown that advanced atherosclerotic lesions in the abdominal aorta of mice can be accurately quantified by magnetic resonance microscopy (MRM). We now extend this technique to non-invasively characterize lesions of varying severity. ApoE-/- mice (n=9) were obtained from atherosclerosis progression and regression studies. Selection criteria (age, plasma lipoprotein profile, and type of diet [chow vs. fat/cholesterol enriched]) were used to identify mice expected to have a wide range of lesion severity. *In vivo* MRM was performed with a 9.4 T MR system. Thirty-two contiguous transverse proton density weighted slices, 500 µm thick and 100 µm in-plane resolution, were obtained in 34 minutes from the abdominal aorta of each mouse. After imaging, mice were exsanguinated and aortic sections taken for analysis. Selected MRM and histological sections were aligned using anatomical landmarks. The aortic wall areas of 20 sections determined by histomorphometry ranged from (mean+SDmm^2) 0.038±0.006 (mild severity; n=7); 0.115±0.076 (moderate, n=7) to 0.61±0.313 (severe, n=6). These results were compared to the areas determined from the corresponding MRM sections. Over the full range of lesion severity, there was a strong correlation (r=0.72; p=0.0003) between the wall areas measured by MRM and histomorphometry. We have shown for the first time that *in vivo* MRM can be used to accurately quantify atherosclerotic lesions of varied severity in the mouse abdominal aorta. This technique will allow the convenient and non-invasive quantitative assessment of serial changes in atherosclerosis in mouse models of disease progression and regression.

Endostatin Overexpression in a Mouse Model of Arterial Injury: The Endothelium as Regulator of Vascular Wall Angiogenesis and Plaque Phenotype.

R. Hutter, B. Sauter, E. Reis, M. Roque, V. Fuster, S.L.C. Woo, and J.J. Badimon. Mount Sinai Medical Center, New York, NY.

Background: Endothelial injury and angiogenesis are considered to play an important role, both in restenosis after percutaneous coronary interventions and plaque vulnerability. Research in this area, however, is limited due to a lack of appropriate *in vivo* models to study the relation between endothelial cell function and development of plaque phenotype. Endostatin is a potent angiogenesis inhibitor which selectively induces endothelial cell apoptosis.

Methods and Results: To evaluate the role of endothelial cell function on neointima formation we overexpressed endostatin in a mouse model of arterial injury. Three groups of C57/BL6 mice underwent femoral arterial denudation and received either a recombinant adenovirus expressing murine endostatin (group 1), a control vector (group 2) or no treatment (group 3). Endostatin gene transfer resulted in high transgene expression levels at 1 week (1011±56 ng/ml) that were still elevated at week 4 (group 1 vs. group 2: 317±35 ng/ml vs. 88±35 ng/ml, p<0.01). Surprisingly, endostatin-vector treatment resulted in increased neovessel formation in the arterial wall and reduced alpha-actin expression in the neointima at 4 weeks after arterial injury (group 1 vs. group 2: 42±6% vs. 59±3%, p<0.01). Moreover, there was a dose-dependent relationship between endostatin serum concentrations and both arterial wall neovessel content (r=0.71; p<0.01) and neointimal alpha-actin expression (r=–0.51; p<0.01). As expected, endostatin overexpression was associated with increased apoptosis of endothelial cells (group 1 vs. group 2: 12±3% vs. 4±3%, p<0.01) and inhibition of re-endothelialization (group 1 vs. group 2: 69±4% vs. 84±4%, p<0.01) in the injured area at 4 weeks.

Conclusions: In summary, impaired re-endothelialization and endothelial dysfunction induced by endostatin overexpression resulted in a shift from alpha-actin-rich and neovessel-devoid neointima, resembling stable plaques, to a new neointima phenotype presenting with features of unstable plaques. Our findings strongly suggest a key role of the regenerating endothelium in controlling the development of arterial lesion phenotype and vascular wall angiogenesis following arterial injury.

A Common Link between Tissue-Factor and Apoptosis in Human Carotid Plaques and Porcine Coronary Arteries Post PTCA.

R. Hutter, B. Sauter, J.T. Fallon, V. Fuster, and J.J. Badimon. Mount Sinai Medical Center, New York, NY.

Background: Tissue factor (TF) has been implicated in the thrombogenicity of ruptured plaques. Apoptotic cells have been postulated as a source for TF. However, there is only limited knowledge about plaque cells exhibiting both TF and apoptosis.

Methods and Results: In serial sections of human carotid atheroma obtained by endatherectomy (n=12) and coronary arteries from a porcine model of PTCA (n=30), we assessed TF and Caspase-3 (CP) antigen distribution by immunohistochemistry and immunofluorescence double labeling. In human carotid plaques TF and CP expression was highest in lipid-rich and myxomatous tissue (24.1±12.7% and 21.1±11.2% of cells, respectively). Double labeling demonstrated an almost overlap of TF and CP expression in these areas. In myxomatous tissue, this cell population stained in addition mostly positive for alpha-actin (smooth muscle cells), in lipid-rich plaque areas mostly positive for CD-68 (macrophages). Fibrous intima tissue revealed significantly less staining for TF and CP. In the porcine coronary arteries 1 day post PTCA cells co-expressing TF and CP were found in the media. Between 2 and 4 weeks post PTCA cells positive for TF and CP were found in the growing neointima in increasing numbers while they disappeared from the media. At all time points, in the adventitia, cellular TF and CP expression was high compared to non-injured control arteries.

Conclusions: Vascular cells co-express TF and CP in human as well as experimental arterial lesions of different vascular origin. In the human carotid plaque cells co-expressing TF and CP were found both in areas of plaque instability (lipid rich) and areas of plaque growth (myxomatous). TF as primary cell associated activator of the coagulation pathway seems to be closely related to apoptotic events in CD-68 as well as alpha-actin positive cells, thereby pointing to a key role of these cells in determining progression and complication of acute and chronic forms of atherosclerosis.

The Effects of Lipid-Lowering Medication on the Recurrence of Ventricular Arrhythmia in Patients with Coronary Artery Disease. M E. Hoffman[1], E. Pe[2], M. Singson[2], B. Dickinson[1], N. Langan[2], J.A. Gomes[2], and D. Mehta[2]. [1]Mount Sinai School of Medicine, New York, NY, [2]Division of Electrophysiology, Department of Cardiology, Mount Sinai Medical Center, New York, NY.

Lipid-lowering medications (LLM) have been shown to reduce mortality in patients with coronary artery disease (CAD). This is probably related to reduction in incidence of cardiac ischemia caused by improvement in endothelial function, stabilization of vulnerable thrombogenic plaques and reduction in platelet activity. The effect of LLM on incidence of ventricular arrhythmia (VA) related to CAD is unknown. We investigated the effects of LLM on the recurrence of sustained VA in patients with CAD and previously documented ventricular tachycardia/ventricular fibrillation (VT/VF).

Methods: 74 patients with CAD, VA and an implantable cardiodefibrillator (ICD) with capability to store electrograms were included in this retrospective analysis. 48 patients (64%) received LLM (Group A), while 26 did not. The choice of prescribing LLM was made by the primary cardiologist. The decision to use LLM did not seem to be based on any specific criteria. The diagnosis of recurrence of VA was based on symptoms and data retrieved from the ICD memory. Recurrence of VA was compared to patient's age, gender, left ventricular ejection fraction (LVEF), presenting arrhythmia, presence of diabetes, use of LLM, digitalis, ACE inhibitors/ATII antagonists, and beta blockers.

Results: Mean follow-up duration was 37.2±33.9 months. VA recurrence was not related to age, gender, presenting arrhythmia, or the presence of diabetes. A higher incidence of VA was seen in patients with lower LVEF. Both in uni- and multivariate analysis, use of LLM was associated with a significant reduction in VA recurrence ($X^2=10.66$, $p=0.003$). There was no correlation between VA recurrence and use of digitalis, ACE inhibitors/ATII antagonists or beta blockers. In our study 4 in Group A and 7 in Group B died.

LLM significantly reduces recurrence of VA in patients with CAD and VT/VF. Independent of other variables this could significantly contribute to reduced cardiac mortality seen with LLM in CAD patients. Thus LLM are important in treating patients with CAD and recurrent VA.

Impact of Limited, Focused and Expedited Echocardiography on Clinical Management of Patients Presenting with Chest Pain and/or Dyspnea to the Emergency Department. S. Harish[1], BS, M.A. Stanizzi[1], BS, L.B. Croft[2], MD, R.E. Shapiro[2], MD, S. Jacobson[3], MD, P.P. Ko[3], MD, T.N. Lee[3], MD, B.K. Richardson[3], MD, A.H. Rubenstein[4], MBBCh, S. Buckley, RMDS, and M.E. Goldman[2], MD. [1]Medical Education, Mount Sinai School of Medicine, New York, NY. [2]Cardiology, Department of Medicine, Mount Sinai Hospital, New York, NY. [3]Emergency Medicine, Mount Sinai Hospital, New York, NY, and [4]Dean's Office, Mount Sinai School of Medicine, New York, NY.

Objectives: We tested the hypothesis that limited, focused and expedited bedside echocardiography in the Emergency Department (ED) can significantly impact the diagnosis and management of patients presenting with chest pain and/or dyspnea.

Background: Limited echocardiography is a rapid, online procedure that can provide accurate diagnoses of patients in the ED and can expedite management, thus improving clinical outcomes.

Methods: Thus far, this study has enrolled 51 consecutive adult patients who consented to an approved IRB protocol and who presented to the ED with chest pain and/or dyspnea on weekdays between 8 am and 6 pm. After the initial clinical evaluation of the patient, the ED physician completed a data form regarding diagnosis and patient management. Then, a brief, focused bedside 2D transthoracic echo was performed using a new, portable, compact ultrasound machine (Acuson Cypress®). Scanning was initially performed by a trained medical student, followed by a board-certified echocardiologist. The limited echo consisted of only 5 views, without Doppler or M-mode. After being presented with the echo findings, the ED physician completed another data form regarding the impact of the echo on the clinical management of the patient.

Results: The limited echo provided valuable information that altered clinical management. The mean performance time of the echo by the students was 9.9 minutes (range 4–20). The ED physicians perceived the echo to be helpful in 76.5% of the cases and to have expedited management in 26.5% of the cases. Comparing the pre-echo and post-echo data forms revealed that the ED physicians changed their initial diagnosis in 41.2% of the cases, changed prescribed medication plan in 31.4% of the cases, altered planned procedures in 21.6% of the cases, and changed final disposition from the ED in 15.7% of the cases.

Conclusion: This study found that a limited, focused and expedited echocardiogram can significantly impact the diagnosis and management of patients with possible cardiac conditions in the ED. GCO # 00-0398

The Feasibility of Training Medical Students to Perform and Interpret Rapid, Diagnostic, Limited Echocardiograms. M.A. Stanizzi[1], BS, S. Harish[1], BS, L.B. Croft[2], MD, R.E. Shapiro[2], MD, S. Jacobson[3], MD, P.P. Ko[3], MD, T.N. Lee[3], MD, B.K. Richardson[3], MD, A.H. Rubenstein[4], MBBCh, S. Buckley, RMDS, and M.E. Goldman[2], MD. [1]Medical Education, Mount Sinai School of Medicine, New York, NY, [2]Cardiology, Department of Medicine, Mount Sinai Hospital, New York, NY, [3]Emergency Medicine, Mount Sinai Hospital, New York, NY, and [4]Dean's Office, Mount Sinai School of Medicine, New York, NY.

Objectives: We tested the hypothesis that it is feasible to train medical students to perform and accurately interpret a limited echocardiogram in a clinical setting.

Background: Echocardiography is a powerful, yet inexpensive and noninvasive diagnostic imaging technique for the management of heart disease. Recently, compact, portable and relatively inexpensive echo systems, with diagnostic imaging capability have emerged. The rate limiting step to widespread exploitation of echo's potential is trained personnel at the immediate contact point with patients as a new generation stethoscope to amplify the history and physical exam. To maximize integration of echo into medical practice, medical students could be trained to perform and interpret cardiac ultrasound studies.

Methods: Following formal IRB approval, two 1st year medical students at Mount Sinai School of Medicine were trained to perform and interpret echocardiographic studies. Students spent 27 hours watching instructional videos, reviewing echo studies, and observing full-length echocardiograms. Hands-on training began by scanning classmates followed by 35 supervised patient exams. Students were trained to obtain a limited 2-D echo, without Doppler and M-mode, using the Acuson Cypress® compact system. The formal study was in the Emergency Department; thus far 68 consecutive patients who consented to the IRB approved protocol have been enrolled. For each subject, the student performed independently a limited echocardiogram and then filled out a data form to assess biventricular and valvular function and the presence and extent of potential pericardial effusions. The student's study was then overread by a board-certified echocardiologist who assessed if the student's echo was diagnostic and if the student had interpreted the echo correctly. Analysis was also divided by sequential thirds to determine the student's progress over the study period. There were 23 subjects in the first and second groups and 22 in the third and last group.

Results: The mean performance time of the echo by the students was 9.9 minutes (range 4–20).

	Overall	1st	2nd	3rd
% Diagnostic Student Echos	94	95	91	95
% Correct Interpretation	76	65	78	86

Conclusion: After a short formal training, students can consistently acquire rapid and diagnostic echocardiograms. However, the student's ability to accurately interpret the echo improves with continued practice. Thus, it is possible and practical to train students to perform and interpret echocardiograms in a reasonable period of time, with a good deal of proficiency. Our findings may have implications for future medical school curricula.
GCO# 00-0398

Prostacyclin Receptor Antibody May Be a Possible Marker for Cardiovascular Disease. N. Kahn, W. Bauman, and A. Sinha. Department of Medicine, [1]Mount Sinai School of Medicine, New York, NY; and [2]Veterans Affairs Medical Center, Bronx, NY.

Cardiovascular disease (CVD) is the most frequent cause of death in adults over the age of 50. The accepted risk factors are smoking (smk), hypertension (hyp), diabetes mellitus (DM) and lipid disorders. Impaired glucose tolerance and DM are more prevalent in spinal cord injured (SCI) persons and they have increased risk of CVD. We have shown that SCI platelets were not hypersensitive to aggregation or resistant to inhibition by prostacyclin (PG12). However, thrombin generation and PDGF release in SCI platelets were not inhibited by PG12-stimulated increase of cyclic AMP. This impaired effect of PG12 was due to a novel circulating antibody (IgG, mol wt 47,000) that specifically blocks the high-affinity PGI2 receptors (kd1=9.1*2.0 vs.7.2*1.1 nM; n1=170*32 vs. n1=23*8 sites/cell) on the platelets without affecting the low-affinity PGI2 receptors. We determined whether a potentially atherogenic IgG was present in subjects with immobilizing conditions and associated cardiovascular risk factors. Plasma samples (50 mg) from subjects were analyzed by PAGE followed by densitometery. The IgG band of mol wt ~47 K was observed in all samples. Compared with controls, OD or optical densities of the band (~47 K) increased in all the samples in smks (n=3) by 47–60%; hyps (n=3) 30–47%; chronic CVD (n=2) 33%; hypercholesterolemia (n=4) 20–33%; lower extremity amputees (n=2) 20%; Type II DM (n=2) 13%. This is the first demonstration of a PGI2 receptor IgG present in SCI and other conditions that are associated with increased risk for cardiovascular disease.

Clinical Immunology

Intestine-Derived Endothelial Cells (HIMECs) Express CD40 Which Correlates with Enhanced Tissue Factor Expression. Ling Shao, David Binion, John Fallon, and Lloyd Mayer. Clinical Immunology, Mount Sinai Medical Center, New York, NY.

CD40 is a critical co-stimulatory pathway regulating T cell:APC interactions. Its expression on B cells, monocytes and dendritic cells is an important component of cytokine production and B cell growth and differentiation. Recent studies have identified the presence of CD40 on human endothelial cells following activation with γIFN or constitutively in skin endothelial cells from patients with SLE. Crosslinking CD40 on these cells results in the production of tissue factor (TF), which might account for the vascular injury seen in these diseases. Intestinal endothelial cells (HIMEC) derived from patients with IBD have been shown to maintain an activated phenotype with enhanced adhesion to a T cell line, MOLT4. To determine whether these lines are potentially capable of interacting with CD40 ligand $(CD40L)^+$ T cells, we analyzed 5 HIMEC lines (1 normal, 2 UC, 2 CD) in early passage for the expression of CD40 using the anti-CD40 mAb 626.1. CD40 expression was constitutive in all cell lines but was not seen in HUVECs. However, the level of expression was roughly one log lower than that seen in human B cell and monocyte lines. Treatment of HUVECS with γIFN induced CD40 expression but had no additive effect on the HIMEC lines. Given the constitutive expression of CD40, we next assessed whether this correlated with TF production. Consistent with the CD40 staining, all lines expressed TF constitutively by immunohistochemistry. We then stained frozen sections of intestinal mucosa from normal and IBD patients. In contrast to the cell line staining, minimal staining of the endothelium was seen in these sections in any tissue when compared to the expression of CD40 by lamina propria macrophages. Thus HIMECs can express CD40 and this does correlate with TF expression despite the limited density of CD40 on the surface. T cells are activated in the bowel and blood of patients with IBD (CD>UC). The interaction of such cells with $CD40^+$ HIMECs might contribute to T cell activation and immunopathology (enhanced coagulation and tissue destruction) seen in IBD.

Expression of Carcinoembryonic Antigen (CEA), Like gp180, Is Reduced in IECs Derived from Patients with Crohn's Disease. L. Bassani, M. Schulder, and L. Mayer. Division of Clinical Immunology, Mount Sinai Medical Center, New York, NY.

Previous studies from this lab have reported that the CD8 ligand gp180, expressed by normal intestinal epithelial cells (IEC) and involved in the activation of suppressor T cells, is reduced or absent in patients with Crohn's disease (CD) regardless of the activity of the disease. More recently we have determined that gp180 is a member of the CEA family of glycoproteins. In order to define whether the defect in gp180 is selective or part of a more global defect in the expression of CEA subfamily members, we stained isolated IECS from 13 normals, 12 CD patients and 10 UC patients with either the anti-gp180 mAb B9 (recognizing a carbohydrate side chain of gp180) or the CEA specific mAb T84.66 (recognizing the protein core - ATCC) and analyzed the percentage stained as well as the number of molecules per cell (measured as mean fluorescence intensity – MFI). Only Epithelial Cell Specific Antigen (FITC-ESA - Biomeda) positive cells were analyzed. In normal IEC gp180 expression was consistently 2–4 fold greater than CEA (MFI 166.18±34 vs 61.06±23) in every sample tasted. The percentage of cells staining was equivalent. As previously reported, the level of gp180 expression was reduced in CD compared to controls (MFI 166.18±13.6 vs 131.06±11.04 – $p<0.05$) while the expression of CEA on these same cells was reduced (61.06 vs 46.08) but did not achieve significance. No difference was seen in specimens derived from areas with active versus inactive disease. IECs derived from patients with UC (active disease) expressed higher levels of gp180 (359.1) than controls (166.18) or CD patients (131.06) (p= NS), while the CEA level was increased (MFI = 175.7) to a greater extent relative to normal controls (p=0.009; UC vs normal). Thus the defect in gp180 expression in CD may be part of a more global defect in the expression of CEA subfamily members. The defect in gp180 expression in UC is not quantitative but rather relates to a defect in protein sorting within the epithelial cell.

Human B Cell Differentiation Factor, 446BCDF, Exhibits Potent Chemotactic Activity for B Cells and Monocytes. Yande Kuang, Thomas Kraus, and Lloyd Mayer. Immunology Center, Mount Sinai Medical Center, New York, NY.

We have previously reported a novel B cell differentiation factor (BCDF), 446BCDF, derived from anti-CD3 mAb(446) stimulated human T cells. This factor was reported to promote Ig secretion in SAC-activated peripheral B cells. Interestingly this cytokine, but not other B cell differentiation cytokines (e.g., IL-2, IL-4 and IL-10), induced a brisk calcium flux in resting B cells. Furthermore, 446BCDF activity was inhibited by pertussis toxin, suggesting that its receptor is G protein coupled. This increase in intracellular calcium as well as the G protein coupled receptor is consistant with chemokine induced signaling in leukocytes. We therefore asked whether 446BCDF has chemotactic activity for B cells. To test this hypothesis, a chemokine assay was performed with either freshly isolated, purified B cells or a 446BCDF responsive EBV-transformed cell line, B7, cells in the presence or absence of 446BCDF.

446BCDF induced a potent chemotactic response in resting B cells (BCDF:210; medium control:46 cells per HFP) and B7 cells (BCDF:152; medium control:48 cells per HFP). Similar results were observed using peripheral monocytes. Pertussis toxin blocked the cell migration induced by 446BCDF in pretreated B7 cells and monocytes. Furthermore, an mAb to 446BCDF, 929, blocked chemotaxis in monocytes as well. The defined MW of 446BCDF is 44Kd, much higher than the typical MW of human chemokines. To ensure that we were not dealing with chemokines contaminating the 446BCDF, we further purified 446BCDF using Centricon 30. The chemotactic activity was found only in high MW fraction. In 446BCDF stimulated T cells, we detected only MCP-1, MIP-1 alpha and IL-8 mRNA. Neither MCP-1 nor MIP-1 alpha had any chemotactic activity for B7 cells. Thus it appears that 446BCDF is a novel B cell and macrophage directed chemokine with unusual biochemical characteristics (high molecular weight).

Lack of IL-10 Receptors on Human Intestinal Epithelial Cells. Thomas Kraus, Asit Panja, and Lloyd Mayer. Immunobiology Center, Mount Sinai Medical Center, New York, NY.

IL-10 has been established as an important cytokine in the regulation of inflammation in the intestinal mucosa. Trial studies are in progress for IL-10 therapy in inflammatory bowel disease (IBD), and there are multiple mouse models of colitis that suggest that IL-10 is a crucial component of the anti-inflammatory network in the gut. However, it is not clear which cells in the gut are responding to this cytokine. To address this question, we analyzed two intestinal epithelial cell (IEC) lines, HT-29 and T84, as well as freshly isolated IECs, for their expression of IL-10 receptor mRNA and for their ability to specifically bind IL-10. We further tested for IL-10-induced STAT activation in these cell lines.

We first analyzed the cell lines for their expression of mRNA that transcribes the two chains of the IL-10 receptor. IL-10R1 is the binding component of the receptor and its expression is limited to cells that have been shown to respond to IL-10, while IL-10R2, the signaling component, is more ubiquitously expressed. Using RT-PCR, we show that IL-10R2 is present in the epithelial cell lines, but IL-10R1 is not detectable. In contrast, we can detect IL-10R1 and R2 mRNA in B cells.

It is possible that these cells bind IL-10 through an alternative receptor. To test for specific binding, we first used a biotinylated IL-10 staining assay. In this assay, all cell lines tested were shown to bind IL-10. However, the staining could not be competed by unlabeled IL-10 nor blocked by a neutralizing anti-IL-10R antibody, suggesting that this staining is nonspecific. We next used ^{125}I-IL-10 in a binding assay. In this assay, we were able to compete for the binding of the iodinated IL-10 with cold IL-10 in B cells, which are known to have IL-10 receptors, but not in the IEC lines or in freshly isolated intestinal epithelial cells. This suggests that there are no specific IL-10 binding proteins on these IEC lines or on primary intestinal epithelial cells.

As further proof that these cells do not specifically bind IL-10, we tested for IL-10-induced intracellular signaling. IL-10 signals through the JAK/STAT pathway. This cytokine has been shown to activate and translocate STAT 1 and STAT 3 to the nucleus. Using Electrophoretic Mobility Shift Assays (EMSA), we cannot detect STAT 1 or STAT 3 activation and nuclear translocation in IL-10 stimulated IEC lines, although we can easily detect STAT activation in control B cells.

These data suggest that the epithelial cells are not the cells directly responsible for the anti-inflammatory effects of IL-10 in the gut.

Endocrinology

At-Risk Pregnancy and the Thyroid — Thyroglobulin Immunization Leads to Allogeneic Fetal Loss. M. Imaizumi, A. Pritsker, P. Unger*, and T.F. Davies. Division of Endocrinology and Metabolism, Department of Medicine, Department of Pathology*, Mount Sinai School of Medicine, New York, NY.

We have previously reported the presence of thyroid autoantibodies as a predictor of increased pregnancy loss. To investigate this further, we have studied the impact of murine experimental autoimmune thyroiditis (EAT) on pregnancy outcome. When CBA/J ($H2^k$) thyroglobulin (Tg)-immunized mice were mated with BALB/c ($H2^d$) males, only 57% (47/83) of pregnant mice delivered live litters compared to >90% of Tg immunized mice mated with syngeneic CBA/J (38/40, $p<0.05$), C3H/HE ($H2^k$) (9/10) or C57BL/6 ($H2^b$) (12/13) males. Furthermore the frequency of thyroiditis was increased in pregnant mice mated with BALB/c males (16/24, 67%) compared to pregnant mice mated with CBA/J males (8/24, 33%) ($p<0.05$). Mitogen-stimulated spleen cells showed that IL-4 secretion was significantly suppressed in pregnant mice mated with BALB/c (12.9±2.0 pg/ml) compared to that in pregnant mice mated with CBA/J (31.2±17.8 pg/ml, $p<0.05$). Furthermore, IFN-(secretion was increased when spleen cells were stimulated by irradiated BALB/c spleen cells (5.7±0.1 ng/ml) while IFN-(was undetectable when they were stimulated by irradiated CBA/J spleen cells. These data showed fetal loss and enhanced Th1 T cell proliferation in CBA/J X BALB/c pregnancies. A concomitant fall in Th2 cells and enhanced lymphocyte reactivity, especially Th1 cell reactivity to alloantigen, was only associated with specific allogeneic BALB/c males. These data demonstrated that $H2^k$ x $H2^d$ pregnancy was an at-risk combination and suggested that paternal MHC may be an important determinant of pregnancy success.

Ligand-Induced Capping of Green Fluorescent Protein (GFP) -Tagged TSH Receptors. R. Latif, P. Graves, and T.F. Davies. Division of Endocrinology and Metabolism, Mount Sinai School of Medicine, New York, NY.

The human TSH receptor (TSHR) is a prototype of G protein-coupled receptors (GPCRs) having large extracellular domains. We have previously shown that TSHRs present in detergent solubilized thyroid membranes existed as monomers, dimers and higher order complexes, some of which were disulfide bonded (Endocrinology 1996, 137:3915). Investigation of these forms of TSHR species within cells has been difficult with standard procedures using antibody tagging, or labeled ligand, due to the paucity of the expressed TSHRs. We chose, therefore, to tag the TSHR with highly sensitive GFP by fusion with the carboxyl terminus of the human TSHR. Cells expressing the fusion protein demonstrated a diffuse plasma membrane fluorescence when excited at 480 nm. Furthermore, the fluorescent receptor was functional, as evidenced by TSH-induced generation of cAMP at a sensitivity of 1000 uU/ml with a maximum stimulation index of 40, suggesting appropriate internal trafficking and correct folding. Time and dose dependent capping of the receptor occurred following TSH stimulation, with a peak capping effect after 15 minutes of stimulation at 37 C. These results open the way for coexpression of TSHRs tagged with GFP variants and the utilization of Fluoresence Resonance Energy Transfer (FRET) for *in vivo* analysis of homodimerization and higher order complex formation.

Gene Interactions Causing Susceptibility for Autoimmune Thyroid Disease in a Large Chinese Family: Results of a Whole Genome Screen. R. Villanueva, Y. Tomer, C. Mao[1], E.S. Concepcion, S. Tucci, G. Estilo, D.A. Greenberg[2], and T.F. Davies. Division of Endocrinology and Metabolism, Department of Medicine, and [2]Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, [1]Division of Pediatric Endocrinology, Harbor-UCLA Medical Center, Los Angeles, CA.

The autoimmune thyroid diseases (AITDs) comprising Graves' disease (GD) and Hashimoto's thyroiditis (HT) develop as a result of a complex interaction between predisposing genes and environmental triggers. In order to dissect the genetic predisposition to GD and HT, we completed a whole genome screen of a large multiplex Chinese-American family with all members from the same region in China. We enrolled 27 family members from 3 generations. Nine members were affected with AITD, 7 had GD and 2 had HT. To determine the informativeness of the family, power calculations were performed. The maximum attainable LOD scores were 5.0 assuming dominant inheritance, and 3.4 assuming recessive inheritance (both at assumed 100% penetrance and one susceptibility gene). Whole genome screening was performed using 400 highly polymorphic and densely spaced microsatellite markers spanning the entire human genome (inter-marker distance < 10 cM). Linkage analysis was performed using two-point and multipoint parametric and nonparametric methods. We identified 2 loci which appeared to be linked to AITD in this family: D11S4191 on chromosome 11 with a maximum LOD score (MLS) of 2.3 and a nonparametric linkage score (NPL) of 6.1, and D9S175 on chromosome 9 with an MLS of 2.0 and NPL of 7.5. In summary, we have identified two new AITD susceptibility loci on chromosomes 9 and 11. These loci were linked with both Graves' and Hashimoto's diseases in one large Chinese-American family. These loci are different from those previously found to be linked with AITD in Caucasians (CTLA-4, AITD-1, GD-1, -2, & -3, and HT-1 & -2). Our results show that even within a single family from a genetically homogeneous population more than one gene may be involved in the genetic susceptibility to AITD. This supports the notion that the AITDs are caused by multiple genes of varying influences.
GCO# 96-277 ME

The Insulin Receptor Gene Region Contains a Gene for Polycystic Ovary Syndrome (PCOS). S. Tucci, W. Futterweit, J.L. Gabrilove, E.S. Concepcion, D.A. Greenberg[1], R. Villanueva, T.F. Davies, and Y. Tomer. Division of Endocrinology and Metabolism, Departments of Medicine and [1]Psychiatry, Mount Sinai School of Medicine, New York, NY.

The polycystic ovary syndrome (PCOS) is one of the commonest female endocrinopathies, affecting 5–10% of women of reproductive age. The disorder is characterized by chronic anovulation, and signs of hyperandrogenism including hirsutism, alopecia and acne. PCOS is associated with obesity and insulin resistance. The pathogenesis of PCOS most likely involves a complex interaction between genetic predisposing factors and environmental triggers. Indeed, epidemiologic evidence shows that PCOS is a familial disorder with a sibling risk of ~ 50%, and several segregation analyses in families with PCOS have suggested a Mendelian dominant pattern of inheritance. However, the genes causing PCOS have not been identified. Several possible PCOS candidate genes have been examined, including CYP19 (aromatase), CYP17, CYP11a, leptin, leptin receptor, insulin VNTR, insulin, and IRS-1. However, none have showed consistent results. Recently, the follistatin gene region was found to be linked but not associated with PCOS, suggesting the possible involvement of the follistatin gene itself. We have studied 85 Caucasian PCOS patients for associations with follistatin, CYP19 (aromatase), CYP17a, and the insulin receptor (INSR) candidate genes. All patients fulfilled the 3 major criteria for PCOS: (1) chronic anovulation; (2) clinical and/or biochemical signs of hyperandrogenism; and (3) exclusion of other etiologies. The control group included 87 age-matched Caucasian women with no clinical evidence of hyperandrogenism. The candidate genes were analyzed using microsatellite markers located near the genes or inside their introns. Microsatellite markers were amplified using fluorescent labeled primers and separated on an ABI-310 genetic analyzer. Our analysis showed no association of the aromatase, follistatin, and CYP17 genes with PCOS. In contrast, the insulin receptor gene marker D19S884 was associated with PCOS (p=0.006, after correction p=0.042). In order to fine map the insulin receptor gene region we analyzed an additional panel of 9 markers spanning the entire INSR gene region. The results showed that only marker D19S884 was associated with PCOS. Marker D19S884 is located 1cM telomeric to the INSR gene. In summary, our results suggest that a susceptibility gene for PCOS is located on chromosome 19p13.3 in the insulin receptor gene region. However, it remains to be determined if this gene is the insulin receptor gene itself or a closely located gene. Since insulin stimulates androgen secretion by the ovarian stroma, it is likely that a gene controlling INSR expression in the ovary could explain some of the genetic susceptibility to PCOS.
GCO# 99-387 ME

Population Comparisons by Obesity and Diabetes Status at Bronx VA. J. Eng* and R. Fuller**. Medical Program* and IRM**, Bronx VAMC, Bronx, NY.

Bronx VAMC's computerized records database was extracted for all patients who had a body mass index (BMI) measurement in FY1999 and secondarily for diabetes (DM). Four groups were categorized by obesity and diabetic status. Obese was de-

	Non-obese Non-DM	Non-obese DM	Obese Non-DM	Obese DM
# Patients	3201	1245	2651	1636
Age, Mean (± STD)	63(15)	68(11)	60(14)	65(12)
BMI, Mean (± STD)	23.4(2.7)	23.7(2.6)	31.3(4.3)	32.3(4.9)
HgbA1c, m(± STD)/nl	4–6.7%	7.6(2.0)		7.7(1.7)
Acute Hospitalizations	1054	486	548	479
Hospitalizations/1000 pts	329	390	207	293
Avg LOS	16.0	12.9	10.5	8.7
BDOC	16903	6265	5762	4187
BDOC/1000 pts	5281	5032	2174	2559

Discharge diagnoses (DXLS) normalized to hospitalizations per 1000 pts.

Congestive Heart Failure	10.3	21.7	2.6	25.7
Atrial Fibrillation	2.2	7.2	3.8	7.9
Cholecystitis/Lithiasis	1.9	0.8	5.3	7.9

fined as BMI > 27 and diabetics as those patients who had ICD-9 codes 250.00 – 250.93 entered for outpatient visits or inpatient stays in FY99. A total of 8733 patients were identified who had BMI measurements, of whom 4287 were obese and 2881 were diabetic. Within these totals, 1636 patients were both obese and diabetic. Profiles of the four populations are compared on the previous page.

Conclusion: Diabetics at Bronx VA have a higher hospitalization rate for congestive heart failure and atrial fibrillation. Obesity is associated with a higher hospitalization rate for cholecystitis/cholelithiasis.

Summary: Population profiling provides evidence to support decision making in health care delivery.

Nitric Oxide: The Second Messenger of Insulin. N. Kahn[1,2], K. Acharya, S. Bhattacharya, R. Acharya, S. Mazumder, W. Bauman[1,2], and A. Sinha[1,2]. Department of Medicine, [1]Mount Sinai School of Medicine, New York, NY; [2]Veterans Affairs Medical Center, Bronx, NY.

Incubation of various tissues, including heart, liver, kidney, muscle, intestine, from mice and human RBC or their membrane fractions, with physiologic concentration of insulin resulted in the activation of a membrane bound nitric oxide synthase [NOS]. Activation of NOS and synthesis of NO was due to the binding of insulin to specific receptors on the cell surface. Lineweaver-Burk plot of the enzymatic activity demonstrated that the stimulation of NOS by insulin was related to the decrease of Km of l-arginine, the substrate for NOS, with simultaneous increase of Vmax. Addition of NG methyl arginine ester [NAME], a competitive inhibitor of NOS, to the reaction mixture completely inhibited the hormone-stimulated NO synthesis in all tissues. Furthermore, NO had an insulin-like effect to stimulate glucose transport and glucose oxidation in muscle, a major site for insulin action. Addition of NAME to the reaction mixture completely blocked the stimulatory effect of insulin by inhibiting both NO production and glucose metabolism, without affecting the hormone-stimulated tyrosine or phosphatidylinositol 3-kinases of the membrane preparation. Injection of NO in alloxan-induced diabetic mice mimicked the effect of insulin in the control of hyperglycemia [glucose—lowering effect of insulin]. However, injection of NAME before the administration of insulin in diabetic-induced and nondiabetic mice resulted not only in the inhibition of insulin-stimulated increase of plasma NO level, but also inhibited the glucose-lowering effect of insulin.

Gastroenterology

Acute Pancreatitis Caused by Afferent Loop Obstruction after Gastrectomy. J. Fares, MD, H. Elfarra, MD, S. Al-Khatatneh, MD, and W. Baddoura, MD. Seton Hall University, School of Graduate Medical Education, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Introduction: Acute pancreatitis due to afferent loop obstruction after Billroth II gastrojejunostomy is extremely rare. It usually occurs many years after the initial procedure. The clinical presentation is variable and nonspecific, leading to a delay in diagnosis with the potential of serious complications. The exact mechanism is not well established; however, it is postulated that increased intraluminal pressure in the afferent loop may promote pancreatic inflammation.

Case Report: A 52-year-old white female presented with one-month history of recurrent episodes of epigastric pain, bloating and back pain, associated with eight pounds of weight loss. Her medical history was significant for cholecystectomy and Billroth II gastrojejunostomy done five years prior for intractable ulcer disease. She denied alcohol consumption or illicit drug abuse. Her medications consisted of Omeprazole, Tramadol, and multivitamins. The physical examination was unremarkable, except for mild abdominal distension and epigastric tenderness. A gastroscopy performed on an outpatient basis showed a distal gastric remnant ulcer and obstruction of the small bowel loops. Therefore, the patient was hospitalized for further evaluation and management. The laboratory investigations revealed a marked elevation of amylase and lipase. The liver function tests showed a tenfold increase in the aminotransferases and alkaline phosphatase levels, with normal bilirubin. The calcium and triglyceride levels were within normal limits. The viral hepatitis serology, antinuclear antibody, antimitochondrial antibody, and anti-smooth muscle antibody were all negative. CT scan of the abdomen revealed obstruction of the afferent loop with evidence of pancreatitis. The patient then underwent a partial gastrectomy with Roux-en-y enteroenterostomy. The postoperative course was uneventful and the patient was doing well on follow-up.

Conclusion: Prompt diagnosis of afferent loop obstruction causing acute pancreatitis is imperative to prevent serious complication. CT scan is considered to be the imaging method of choice for diagnosis. Conservative management is invariably fatal and surgical intervention is clearly indicated.

A Case of Acute Necrotizing Pancreatitis Complicating Salmonella Enteritis. H. Elfarra, MD, J. Fares, MD, S. Al-Khatatneh, MD, and W. Baddoura, MD. Seton Hall University School of Graduate Medical Education, Division of Gastroenterology, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Background: Infectious causes of acute pancreatitis are rare. It is still unusual for certain bacterial pathogens like salmonella to present with acute pancreatitis. Till now there is no general agreement about the possibility that pancreatitis could be caused by salmonella infection. The most common intra-abdominal localized infections due to salmonella are cholecystitis and splenic abscess. We report a rare case of acute necrotizing pancreatitis caused by *Salmonella paratyphi A*.

Case Report: A 23-year-old Hispanic male with no significant past medical history presented with a two-day history of severe abdominal pain, vomiting and bloody diarrhea two days after he ate in the park with his wife. The patient denied drinking alcohol or taking illicit drugs, and also denied previous similar attack. He was not on any medications. Examination was remarkable for dehydration and upper abdominal tenderness. Initial laboratory data showed WBC 22,000, amylase 3200 U/L and lipase 2800 U/L, BUN 48 mg/dL and creatine 1.2 mg/dL. Serum calcium, liver enzymes, bilirubin and triglycerides were all normal. He was admitted and was given aggressive intravenous fluid hydration. Abdominal ultrasound was unremarkable. Abdominal CT with intravenous contrast was consistent with necrotizing pancreatitis. Stool and blood culture were both positive for *Salmonella paratyphi A*. He was started on intravenous Levofloxacin 500 mg daily on the second day of admission. On the seventh day of admission he became asymptomatic and all of his laboratory data normalized by the third week.

Conclusion: Salmonella pancreatitis is rare. In the presence of bacteriological evidence of salmonella and diarrhea with high amylase salmonella should be considered as a likely cause of pancreatitis. Intravenous antibiotic in this case is warranted. Cholecystectomy in such cases is still controversial in the absence of gallstones.

Endoscopic Band Ligation of Bleeding Duodenal Varices. S. Al-Khatatneh, MD, J. Fares, MD, H. Elfarra, MD, and W. Baddoura, MD. Seton Hall University, School of Graduate Medical Education, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Introduction: Bleeding from varices outside the gastroesophageal region is an uncommon complication of portal hypertension. These ectopic variceal bleedings, such as duodenal, are often massive and life threatening. Therefore, a prompt recognition of this condition with early intervention is imperative. Different modalities of treatment have been described.

We report a case of duodenal variceal bleeding treated successfully by endoscopic band ligation.

Case Report: A 34-year-old female with a history of alcoholic liver disease and type II diabetes mellitus was hospitalized for multiple episodes of hematemesis and melena associated with dizziness and generalized fatigue. On physical exam, she had stable vital signs and no stigmata of liver disease. The examination was otherwise unremarkable. The initial hemoglobin was 6.7 gm/dl with a hematocrit of 20.2% and an MCV of 83. There was thrombocytopenia with a normal coagulation profile. The aminotransferases were normal, but marked hypoalbuminemia was noted. The viral hepatitis panel was negative. Rapid volume replacement was initiated and intravenous Octreotide and Famotidine were started. She also received multiple blood transfusions. An urgent esophagogastroduodenoscopy (EGD) demonstrated gastritis and erosive duodenitis with no evidence of gastroesophageal varices or stigmata of recent bleeding. On the second day of hospitalization, the patient again started having hematemesis. A second EGD was then performed; it revealed a large varix in the second part of the duodenum, with a cherry-red spot and some blood oozing. The varix was successfully band ligated. The patient had no subsequent bleeding episodes and her hemogram remained stable.

Conclusion: Recognition of bleeding duodenal varices is critical, given the potential of recurrent bleeding and its attendant risks. Endoscopic band ligation offers an effective modality of treatment and appears to be safe.

Nonsteroidal Anti-inflammatory Drugs as Chemopreventive Agents in Colorectal Tumors. Ramaraju GA, Daniel SJ, and Mokuolu AO. Department of Medicine, North General Hospital, New York, NY.

Background: The third leading cause of cancer death in the United States is colorectal cancer. Animal studies have shown aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) to be effective chemopreventive agents in carcinogen-induced colorectal tumors. In human studies too there is evidence that exposure to NSAIDs leads to decrease in colorectal tumors. However none of these studies have investigated the role of NSAIDs in African-American and Latino populations with colorectal tumors.

Aim: The purpose of this study is to investigate the role of NSAIDs as chemopreventive agents in African-American and Latino patients with colorectal tumors.

Methods: The association between the use of NSAIDs and colorectal tumors was examined in a retrospective review of charts of 129 patients who had either adenomatous polyp or cancer of the colon, and compared with 112 age and sex matched controls in a case control study. All participants had undergone colonoscopy at North General Hospital between 1998 and 1999. Information on exposure to NSAIDs was obtained from chart review. Exposure was defined as the use of NSAIDs for at least 1 year prior to colonoscopy. The rate of exposure to NSAIDS was compared in patients with or without colorectal tumors. Using chi square analysis the odds ratios (O.R.) were calculated according to exposure and non-exposure to aspirin or NSAIDs.

Results: 745 colonoscopies done revealed 129 patients (17.3%) with completed information. The mean age was 67.5 years and 54% were women. The study population consisted of 90% African Americans and 10% Latinos.

Twenty-nine (29) patients had colorectal cancers and 100 patients had adenomatous polyps of the colon. 36 patients (27.5%) with colorectal tumors compared to 42 (57.7%) without tumors were on NSAIDs (O.R. = 1.55; 95% Confidence Intervals [CI] 0.90–2.66). 32 patients (32%) with adenomatous polyps compared to 42 (57.5%) without polyps were on NSAIDS (O.R. = 0.78; 95% CI 0.44–1.38). 4 patients (13.7%) with colorectal cancers compared to 42 (57.5%) without colorectal cancers were on NSAIDS (O.R. = 0.27; 95% CI 0.09–0.82). The exposure to NSAIDs was associated with reduced prevalence of colorectal tumors but was only statistically significant in colorectal cancers and not in adenomatous polyps of the colon.

Conclusions: In our study the use of NSAIDs was noted to have a primary role in preventing colorectal cancers.

Chronic Nitric Oxide Treatment Reverses the Adverse Effects of Nicotine on Ethanol-Induced Gastric Mucosal Injury. MA Korsten, JJ Ma#, YC Ma, ZY Guo, CX Li, and QB Zhang. Gastroenterology Program, Bronx VAMC, Bronx, NY and #Department of Pharmacology, Beijing Medical University, PRC.

Background: Nicotine increases the severity of experimental gastric ulceration, possibly by reducing gastric mucosal blood flow (GMBF) and mucus production. Since both these parameters can be improved by nitric oxide (NO), we assessed whether an NO donor could ameliorate the detrimental effects of nicotine in a rat model of ethanol-induced gastric mucosal injury.

Methods: A nicotine solution (50 μg/ml in drinking water) or tap water was administered ad lib for 20 days to male SD rats (160–180 g, 8 rats/group). In the first series of experiments, two doses of an NO donor (isosorbide dinitrate, 10 mg/kg, po) were given 60 min. and 10 min. before preparation of *ex-vivo* gastric chambers. The chambers were exposed to 1.5 ml 80% v/v ethanol solution for 15 min.

Results: (Expressed as mean ± SEM) #1: Mucosal damage (lesion size expressed as % of total mucosal area: Tap water 8.4±0.7; Nicotine 14.9±1.5*; Nicotine+NO donor 13.7±1.7*. Gastric mucus content (Alcian blue method, mg/g): Tap water 186±16; Nicotine 132±12*; Nicotine+NO donor 139±14*. GMBF (measured by the laser Doppler flow technique in arbitrary units): Tap water 34±2.6; Nicotine 24±2.1*; Nicotine+NO donor 25±2.4*. The results of this first experiment indicate that nicotine intensifies ethanol-induced gastric injury and that an NO donor fails to protect when given acutely. In a second series of studies, rats were administered a nicotine solution or tap water for 20 days, after which the nicotine was withdrawn and replaced by tap water for 10 additional days. Isosorbide dinitrate (10 mg/kg po TID) was administered during these last 10 days. Results #2: Mucosal damage: Tap water 7.8±0.9; Ex-nicotine 10.4±1.0*; Ex-nicotine+NO donor 7.6±0.8. Mucus content: Tap water 200±18; Ex-nicotine 154±15*; Ex-nicotine+NO donor 192±20. GMBF: Tap water 35±2.8; Ex-nicotine 27±2.4*; Nicotine+NO donor 33±2.2. These results indicate that the effects of nicotine persist for at least 10 days after nicotine is withdrawn but that chronic NO can attenuate these effects.

Conclusion: Neither nicotine cessation alone nor acute NO administration reverses the deleterious effects of nicotine on ethanol-induced gastric mucosal injury. However, after nicotine cessation, chronic NO can completely abolish the effects of nicotine on ethanol-induced changes in mucus, GMBF and mucosal integrity. *$p<0.05$ vs. tap water control group.

General Internal Medicine

The Potential Value of Bone Density Screening in Peri- and Post-menopausal Women. H.K. Rambaran[1,2], V.A. DeBari[1] and N. Rambaran[1,2]. Department of Medicine[1]/Pediatrics[2], St. Joseph's Hospital and Medical Center, Paterson, NJ.

Metabolic bone diseases (MBD), osteoporosis and osteopenia, are a major health problem in women who are approaching or who have reached menopause. Rapid screening devices for bone density have enormous potential to avert chronic MBD in this population. However the following questions arise: Who should be subjected to this screening procedure, and is screening of value in women who are at only normal risk for MBD? In this study, we used an evaluation instrument to assess the level of risk and used a peripheral densitometer (PIXI, Lunar Corp.) to evaluate the presence or absence of MBD. Eighty peri- or post-menopausal women between the ages of 44 and 85 were given questionnaires. Based on the results of this evaluation, 22 were found to be at "above-normal" risk for MBD. All subjects were then subjected to the PIXI scanning procedure. It was found that among the patients with above-normal risk scores 11/22 or 50% had MBD. In the group at "normal" risk 17/58 or 29% had MBD. These differences were compared using a parametric inferential method (normal difference or "Z" test) and were found not to be statistically significant (Z=1.5; p=0.134). Among the 28 patients with MBD, 14 had osteoporosis and 14 had osteopenia by PIXI scoring parameters. Five in the osteopenia group and 6 in the osteoporosis group had been evaluated as "above-normal" risk. These data suggest that even women who seem not to be at abnormally high risk, may well benefit from bone density screening for surveillance and early intervention of MBD.

Abnormal Persistent Elevation of Alanine Aminotransferase (ALT). A. Patel, M.D. Internal Medicine Resident, MSSM (Elmhurst) Program, Elmhurst Hospital Center, Elmhurst, NY, and A. Lyman, M.D, MSCM. Faculty, Department of Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Introduction: The increased use of aminotransferase assays in health surveys and screening (e.g., health insurance, blood donor screening) has led to the "accidental" discovery of a large number of persons with pathological liver function tests (LFT) (1–5).

The majority are asymptomatic. The positive predictive value of a single abnormal aminotransferase for chronic liver disease is only 10–15%. During blood bank screening, 33% of patients were found to have an elevation of ALT. The aim of this study is to investigate the frequency, final diagnosis, usefulness of liver biopsy and the clinical course of patients encountered in Elmhurst Hospital Center with persistently (>3 months) elevated ALT.

Methods: All patients with abnormal LFT were obtained from computerized medical record system during the period of June 1998 to December 1998. All adult patients with a first elevated ALT >1.5 X upper normal limit (during the study period) who then had persistent elevations of ALT for at least 3 months were included in the study.

Results: 1361 patients had abnormal ALT. 682 patients (50%) had ALT >75. 26 (41%) were Hispanics, 14 (23%) were of unknown race/ethnicity and 9 (15%) were South Asians. Females {35(56.5%)} outnumbered males {27(43.5%)}. 41 patients (68%) were < 59 years old. No standard documentation regarding alcohol consumption (heavy, dependent, "ex-heavy", yes, number of cans/week, occasional) was found. No record of any occupation (including health care worker or manufacturing) related to liver injury was found. One patient (1.5%) admitted using IV drugs in the past. Record review revealed two patients (3%) had received blood transfusions. AIDS and diabetes were common comorbidities associated with chronic hepatitis. Hepatitis C (24%), fatty liver (16%), hepatitis B (15%), drug toxicity (11%), alcohol (8%) and pregnancy (4%) were the causes of chronic hepatitis. Eleven (17%) patients were referred to liver clinic and 3 (27%) were advised to undergo liver biopsy. None of the patients underwent liver biopsy, either refusing or having been lost to follow-up.

Conclusion: Hepatitis C and B are frequent causes of chronic hepatitis. Further study is needed to determine effective means of increasing acceptance of care. Standardized documentation of alcohol consumption levels, including ascertainment of binge drinking, and of occupation should be encouraged.

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Antiretroviral Therapy in Elmhurst Hospital Center (EHC) HIV Clinic: Risk Factors for Virologic Failure. M. Marin, MD, Internal Medicine Resident, MSSM Elmhurst Program, and A. Lyman, MD, MSCM, Faculty, Department of Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Highly active antiretroviral therapy (HAART) has produced a dramatic reduction in morbidity and mortality rates associated with HIV-1 infection in the US (1). In clinical trials, combinations of protease inhibitors (PI), nucleoside analogues (NA), and non-nucleoside reverse transcriptase inhibitors (NNRTI) have reduced plasma HIV-1 RNA levels to less than 400/ml in 60–90% of patients (2). A study done in a large urban clinic in Baltimore concluded that unselected patients in whom HAART is started in a clinic setting achieve viral suppression substantially less frequently than do patients in controlled clinical trials (3). The present study was done to determine factors associated with failure to suppress HIV RNA levels in a cohort of patients treated with anti-HIV therapy who had a first visit to HIV Clinic-EHC from July 1997–June 1999. Demographic variables, adherence to clinic appointments, and plasma HIV-RNA levels (VL) were obtained from clinic charts. Adherence to clinic appointments was recorded as a percentage of scheduled appointments that were attended. Patients were assigned to mutually exclusive risk factor categories. Response to treatment: good response if all viral loads measured after at least one month of treatment were less than or equal to 400 copies/ml; virologic failure if any viral load measured after at least one month of treatment was more than 400 copies/ml. A total of 82 patients was identified; 33 patients did not meet inclusion criteria. A total of 49 patients was included in the study. Male: 76%, Hispanic ethnicity: 67%. VL were undetectable in 45% of patients during the follow-up period. Higher rates of virologic failure were found in: age 35–44(74%), male (59%), African-American ethnicity (67%), homosexual exposure (64%), not married (63%), level of education high school or less (65%), visits attended less than 90% (66%). Treatment outcomes at EHC were better than those achieved in a HAART study (1) in an inner-city hospital. Due to the small sample size, none of the analyses were statistically significant. A larger study is needed to further explore predictors of virologic failure.

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Prostate Carcinoma at Elmhurst Hospital Center (EHC). A. Mojaverian, MD, Internal Medicine Resident, MSSM (Elmhurst) Program, Elmhurst Hospital Center, Elmhurst, NY, and A. Lyman, MD, MSCM, Faculty, Department of Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Approximately 60% of patients with serum prostate specific antigen (PSA)>10 have prostate cancer. Many other conditions (benign prostatic hypertrophy (BPH), prostatitis, prostate infarct and prostatic intraepithelial neoplasia [PIN]) cause an elevated PSA (1, 2). The American College of Preventive Medicine recommends against routine population screening with DRE and PSA; however, the American Urological Association and the American College of Radiology recommend annual DRE and PSA screening at age 50 and annual PSA screening at age 40 for men with a positive family history of prostate cancer and for African-Americans (3). The reported positive predictive value of PSA in asymptomatic men is only 28–35%; if combined with digital rectal exam (DRE), this increases to 49%. A retrospective cohort study of patients diagnosed with prostate cancer at EHC from 1995–1997 was conducted. A list of patients was obtained from the Tumor Registry; charts were reviewed for demographic and clinical variables. Data were tabulated with Excel software; odds ratios and chi square analyses were performed with EpiInfo software. Seventy-five charts were eligible for review. Mean age was 68.8 (range 38–95); race/ethnicity: White 23 (31%), African-American 17 (23%), East Asian 3 (4%), South Asian 9 (12%), Hispanic 19 (25%), unknown 3 (5%). On DRE, 15 (20%) had (+) nodule in the prostate, 41 (54%) had (–) nodule, and for 17 (23%) the result of the DRE was not found in the chart. Histologically, 64 patients (85%) had adenocarcinoma, 3 (4%) had PIN, and 8 (11%) had no biopsy. Thirty-four patients (47%) were diagnosed by screening PSA. The distribution of PSA level was: PSA<4: 0%, PSA 4–9.9: 30%, PSA 10–20: 24% PSA>20: 29%, and 16% not mentioned. In stage 1, only 8% of patients had PSA>20; in stage 2 about 15% had PSA>20; in stage 3, approximately 50% had PSA>20, and in stage 4, 59% had PSA>20. The distribution of PSA level by race/ethnicity varied, and 35% of Whites, 41% of African-Americans, and 21% of Hispanic patients had metastasis (stage 4). By ethnicity, the highest proportion of prostate carcinoma cases were in African-Americans, and they were more likely to have metastatic disease, consistent with the literature. Hispanics tended to have lower PSA levels and less invasive disease; however, statistical significance could not be assessed because of small subgroup sizes. Additionally, this may have been confounded by age.

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Risk of Endoscopy during Tissue-Friable Period in Patients with Caustic Ingestion. S. Bagae, MD, Internal Medicine Resident, PCIM Elmhurst Program, V. Gumaste, MD, Chief, G.I. Clinic, and A. Lyman, MD, MSCM, Faculty, Department of Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

5000–15,000 cases of caustic ingestion are reported in the United States (1). Endoscopy, a standard diagnostic tool in the management of caustic injury, should be performed within 12 hours; numerous case series demonstrate that the procedure is safe during this period. Subsequently, there is a period of wound softening beginning as early as 12 hours post-injury and lasting about 2 weeks, during which it is considered unsafe to perform endoscopy due to friability of the tissue (2). A retrospective cohort study was done at Elmhurst Hospital Center to evaluate the risk of endoscopy during the tissue-friable period. All patients who underwent endoscopy from 11/95–6/99 with a diagnosis of caustic ingestion were selected, and inpatient, emergency room and endoscopic reports were reviewed. Main outcome measure: complication in relation to timing of endoscopy (any complication occurring in periendoscopic period - perforation, hemorrhage or any antecedent event during analgesia or sedation in preparation for the procedure). Tabulations were done by hand and odds ratio and chi-square analyses were conducted using EpiInfo software.

Thirty-four patients with the diagnosis of caustic ingestion were found in the gastroenterology division's endoscopic computerized database; 30 charts (88%) were available for review. Data for 22 patients (73%) were included in the study; 8 patients (27%) did not have caustic ingestion. Age: 15–81 years (mean = 32.6 years). In eighteen (82%) the injury was produced after intentional ingestion, 11 (50%) had documented underlying psychiatric diagnoses, 3 (14%) had history of substance abuse. Timing of endoscopy: 11 (50%) of the 22 patients had endoscopy earlier than 12 hours; 9 (41%) had endoscopy from 12 hours to 2 weeks post-injury (high-risk period); the remaining 2 (9%) had endoscopy after 2 weeks. Endoscopic findings; 14 patients (64%) had normal to mild lesions (less than grade 2b lesion); 7 (32%) had moderate to severe endoscopic findings (grade 2b and higher). One patient had an incomplete study. In those with normal to mild endoscopic findings, 12 (86 %) were discharged within twenty-four hours. There were no complications, including among those who had endoscopy during what is considered the high-risk period (OR=0, p=1), but the analysis was not valid because of small expected values. A larger sample size is needed (e.g., multicenter study) to further evaluate this question.

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Cervical Dysplasia in Patients with Atypical Squamous Cells of Undetermined Significance (ASCUS) Diagnosis at Elmhurst Hospital Center (EHC). S. Mariano, M.D. Internal Medicine Resident, MSSM (Elmhurst) Program, S. Rathnam, M.D., Clinical Assistant Professor, Department of Ambulatory Care, and A. Lyman, M.D, MSCM. Faculty, Department of Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Objective: To determine the rate of dysplasia in patients with a Pap diagnosis of ASCUS and to identify clinical predictors of dysplasia in these patients.

Methods: A retrospective cohort study of patients at EHC with a diagnosis of ASCUS for the period of January 1–31, 1999 was conducted. Patients were seen at different clinical services including OB-GYN, internal medicine, adolescent clinic and inpatient service. Medical records of patients with ASCUS diagnosis for the study period were obtained from the records of the Cancer Detection Clinic of OB-GYN. Data were gathered through chart review and by using the HDS computer system. Age, ethnicity, age at first sexual intercourse, history of sexually transmitted diseases (STD), history of previous abnormal Pap, colposcopy findings and follow-up were recorded, and frequencies tabulated by hand. Odds ratios were calculated and statistical significance assessed by chi-square analysis or Fisher's exact test.

Results: There were a total of 80 ASCUS cases; 68 charts (85%) were available for review. 46% of ASCUS cases proved to have abnormal colposcopic findings (17% CIN I, 8% CIN II, 8% CIN III and 13% HPV). Only age ≤35 yrs and positive smoking history were associated with pathologic colposcopy results (70%≤35 vs 28%>35 yrs), OR=5.83 (95% C.I.=0.74, 54.32 and 100% of smokers vs 35% of nonsmokers, OR=undefined, p=0.0737, respectively). Subdividing ASCUS into "unqualified", "favor reactive" and "favor dysplasia" failed to demonstrate any statistical association with colposcopy findings. Similarly, a history of STD, multiple sexual partners and previous abnormal Pap were not associated with abnormal colposcopic findings. On follow-up, either by Pap alone or by Pap plus colposcopy, 60–63% of the ASCUS cases reverted back to benign Pap/colposcopy findings. However, a substantial proportion of these women (37–40%) had persistent abnormal results.

Conclusion: A diagnosis of ASCUS defines a group of women at increased risk of developing a significant cervical lesion. Age ≤35 yrs and positive smoking history are possibly predictors of dysplasia in this population. Twenty-six patients (39%) were lost to follow up. Importance of medical surveillance must be stressed by clinicians with these patients.

Risk of Developing Lung Cancer in Non-smokers at Elmhurst Hospital Center (EHC). A. Aziz, M.D., Internal Medicine Resident, MSSM Elmhurst Program, and A. Lyman, M.D., Faculty, Department of Ambulatory Care.

Background: According to Cancer Data Base Report on lung cancer 1996, lung cancer is the most common cause of cancer deaths in the United States and the most common cancer among U.S. men and women. Age specific rates for 1983–1987 for each major histologic type were at their maximum at 70–74 years. In recent years, adenocarcinoma was the most frequent histologic subtype for all races and sexes combined. Cigarette smoking is the most common cause of lung cancer, while environmental tobacco smoke (ETS, involuntary or passive smoking) is the major risk factor for non-smokers.

The lifetime risk of nonsmokers for lung cancer in the U.S. is 1 in 357 (Clinics in Chest Medicine – March 1993). In 1993, the U.S. Environmental Protection Agency reported that passive smoking is responsible for approximately 3,000 cancer deaths annually in non-smokers. They also recommended against screening for early detection of lung cancer.

Objective: To evaluate the risk of lung cancer in nonsmokers and to determine the relationship between age, sex, ethnicity and histologic type of lung cancer.

Design: Retrospective cohort study.

Setting: Elmhurst Hospital Center, Department of Medicine.

Methods: Identification of patients with lung cancer from January 1994 to June 1999 was obtained from tumor registry board. Data was collected from medical records by reviewing patient charts. Total number of patients with lung cancer was 195. Only 23 patients (12%) were nonsmokers and 21 of the 23 charts were available for review.

Results: Adenocarcinoma was found to be the most common histologic type of lung cancer in nonsmokers (13 patients [62%]). Two thirds of the patients were female, and most were of Hispanic background. Mean age of presentation was 61 years. Most commonly presented symptoms were cough and hemoptysis. Only 3 patients had documentation of ETS while the risk factors for other patients were not mentioned in the chart. Patients mostly presented at advanced stage of disease (Stage IV) and half of them (12 out of 23 patients) died during $5^1/_2$-year period.

Conclusion: That the risk of developing lung cancer in nonsmokers is most likely secondary to environmental tobacco smoke was not proven by this study, as information was limited and sample size was small. That adenocarcinoma is the most prevalent lung cancer was strongly supported by this study.

Anticoagulation in Patients with Atrial Fibrillation, Medical Primary Care Clinic (MPC), Elmhurst Hospital Center (EHC). N. Sajnani, MD, Internal Medicine Resident, MSSM Elmhurst Program, S. Tejwani, MD, Faculty, Department of Ambulatory Care, Elmhurst Hospital Center, A. Lyman, MD, MSCM, Faculty, Department of Ambulatory Care.

Atrial fibrillation is the most common sustained arrhythmia and is associated with a significant risk of stroke. Numerous randomized trials have conclusively demonstrated that adjusted dose warfarin is highly efficacious in stroke prevention. (Ann Intern Med Vol 131. No. 7 Oct. 5, 1999). Despite this, several studies have demonstrated that "real world" use of warfarin is only 15–44% in patients with atrial fibrillation without contraindications (Arch Intern Med.Vol.160. Jan 10, 2000).

Aim: To determine whether eligible patients with atrial fibrillation followed in MPC were anticoagulated appropriately to prevent stroke, whether nonanticoagulated patients were prescribed aspirin, and what proportion of International Normalized Ratios (INR) were in the therapeutic range.

Methods: This study is a retrospective cohort study in which all patients with atrial fibrillation followed in MPC at EHC from Jan 1997–Dec 1999 were identified and a random sample was selected using random numbers generated by EpiInfo software.

Charts were reviewed to evaluate use of warfarin, use of aspirin in those who were not on warfarin, documentation in the chart about potential contraindications of warfarin in patients who were not anticoagulated, and last three serial INR'S to determine their therapeutic range. Results were tabulated by hand. Odds ratio and chi-square analyses were performed to examine relationships between demographic variables and refusal of warfarin, loss to follow-up, and 0–1 therapeutic INR vs 2–3 therapeutic INR.

Results: One hundred thirty (130) patients were eligible. Medical records of a random sample of 66 patients were selected, and 62 patients were included in the study. The mean age of the patient population was 72 years. 33 (53%) were women and 29 (47%) were men. Race/ethnicity: white 26 (42%), Hispanic 25 (40%), Asian 6 (10%), and black 5 (8%). 37 (60%) patients were on warfarin, 25 (40%) were not. Of those who were not anticoagulated, 22 (88%) were on aspirin and 3 (12%) were not. 37 (48%) had > 1 stroke risk factor and 25 (52%) had ≤ one stroke risk factor. Of the 40% who were not on warfarin, 20 (80%) patients had potential contraindications to warfarin and 5 (20%) patients refused warfarin. There were no statistically significant differences according to gender, race or age for refusal of warfarin, number of therapeutic INR'S or loss to follow-up.

Conclusion: Prevalent use of warfarin among eligible patients, i.e., without any contraindication, was 88%, a percentage that is much higher than other recent estimates among outpatients, but the percentage of INRS in the therapeutic range on two or more of the last three clinic visits was 35%. Futher studies and measures to improve quality of anticoagulation are needed for better outcome to prevent stroke in atrial fibrillation.

Technique of Metered-Dose Inhaler (MDI) Use by Patients with Asthma. Y. Talalaev, MD, Internal Medicine Resident, PCIM Elmhurst Program, and A. Lyman, MD, MSCM, Faculty, Department of Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

The technique of patient MDI use is frequently suboptimal. Patient education in correct usage is time consuming and often non-productive (1). Some practitioners are unable to demonstrate correct technique (2) and may assume that patient education has been previously done by other personnel. Testing of this skill is frequently not done (3).

Aim: 1) To evaluate patient education and ability to correctly use MDIs; 2) to determine the most common mistakes and ways to improve performance; and 3) to assess if performance can be improved using simple written instructions (requiring minimal additional office visit time).

Methods: Adult patients with asthma who were seen in the Medical Primary Care Clinic or the Emergency Room, who had no physical limitations impairing performance (e.g., stroke, arthritis, dementia) and no acute respiratory distress were included in this study. Patients were observed executing seven steps: 1) shaking the MDI, 2) removing the cap, 3) positioning the MDI, 4) exhaling, 5) starting to inhale while simultaneously activating the inhaler, 6) continuing to inhale, 7) holding breath before exhaling. Following this, patients were given simple one-page English instructions on correct technique, given sufficient time for reading and comprehension of the material, and then asked to demonstrate technique again. One point was given for each correctly performed step. Results of the two trials were compared.

Results: Sixteen patients were included in this study. The most common mistake was step requiring hand-breathing coordination (steps 4–6). These steps were also the most difficult to correct, but were eliminated if a spacer device was used. Only 12.5% of patients were able to perform the technique correctly prior to reading study material; success then increased to 37.5%. 25% of patients stated they were never educated by any health professional in correct inhaler use, although all had a diagnosis of asthma for greater than four years. Most of the education (37.5%) was done by PMD (no patient reported education by pharmacist). Greater number of years of MDI use did not lead to appreciable difference in performance (4.3 vs 4.6). Patients using MDI > 2 times daily had a higher average score (4.9 vs 4.0).

Conclusions: 1) Provision of simple instructions on MDI technique use may improve performance. 2) Most patients lacked adequate education. 3) Use of a spacer device may eliminate the most frequent mistakes in technique, which were also the most difficult to correct.

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Risk Factors for Symptomatic Coumadin Toxicity in Patients Followed at Elmhurst Hospital Center (EHC) Coumadin Clinic (CC). Maria Oca, MD, Primary Care Internal Medicine Residency Program, Andrea Lyman, MD, MSCM, Department of Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Objective: To determine risk factors predictive of symptomatic Coumadin toxicity in patients followed in Coumadin Clinic (CC).

Introduction: Oral anticoagulation therapy is the mainstay of treatment for many common conditions. Despite its effectiveness, its therapeutic window is narrow. The CC at EHC provides a central facility for monitoring long-term outpatient anticoagulation therapy. More than 700 patients—the vast majority of EHC patients on Coumadin therapy—were followed in CC during 1999. For these patients, a registered nurse and a cardiology fellow review the indications for therapy and determine the therapeutic range of INR. Patients with INR values outside the therapeutic range are contacted by telephone, telegram or in person and instructed to adjust their Coumadin dosage. Patients are admitted to EHC for an INR≥10 even if asymptomatic.

Methods: A retrospective analysis of patients admitted to EHC with Coumadin toxicity from November 1995 to November 1999 was performed. Coumadin toxicity was defined as INR ≥10, or occurrence of bleeding. Age, race/ethnicity, language, sex, diet, indications for anticoagulation, duration of anticoagulation, frequency of clinic visits, co-morbid medical conditions, other medications, INR on admission and reason for admission were obtained from the medical record. Frequencies were tabulated by hand and odds ratios and 95% confidence intervals [OR (CI)], or chi-square analyses or Fisher's exact tests were performed with EpiInfo software.

Results: Of 135 patients admitted with a diagnosis of Coumadin toxicity, 48 were followed in CC and were included in the analysis. Thirty-four charts (71%) were available for review. Race/ethnicity distribution: Hispanic 12 (35%), East Asian 7 (20%), Caucasian 6 (18%), South Asian 4 (12%), African-American 2 (6%), not documented 3 (9%). Language spoken: English 19 (55%), Spanish 8 (23%), Korean 4 (11%), Chinese 3 (9%), Bengali 1 (3%). The risk of being admitted for bleeding as opposed to asymptomatic toxicity was significantly higher for non-English speakers [OR = 10.67 (95% CI, 1.68, 78.83), p=0.0024]. Patients 65 or older had a non-significantly greater risk of symptomatic toxicity [OR = 1.14 (0.23, 5.66)]. This was also true for non-Caucasians [OR = 2.82 (0.23, 150.44)].

Conclusion: Not speaking English was significantly associated with admission for symptomatic Coumadin toxicity. No other factor studied was statistically significant, possibly due to inadequate statistical power. We are not aware of previous studies investigating language barrier as a risk factor for Coumadin toxicity; a prospective study with a larger population size should be undertaken. Since EHC CC serves a multiethnic population, it is important to consider providing multilingual information, including directions for Coumadin use, side effects of medication, nutritional information, etc., and evaluating its impact.

The Didactic Value and Clinical Impact of a Poetry Discussion Workshop in Housestaff Education. Lawrence M. Reich, MD. Department of Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Background: In recent years, medical curricula have been enhanced by inclusion of the discipline of literature and medicine. Structured discussions of medically-relevant poetry and prose can serve several didactic functions, such as teaching communication skills, framing discussions of medical ethics, facilitating the understanding of clinical narratives, sharpening deductive reasoning skills, enhancing the experience of the physician and the trainee and teaching them to think about illness, disease, and patient care from a more flexible perspective. Few studies have tried to demonstrate a clinical role for such discussions.

Aim: A monthly poetry discussion workshop was introduced into the curriculum of the Primary Care Internal Medicine Residency Training Program at Elmhurst Hospital Center. Poems dealing with issues of the doctor-patient relationship and the experiences of physicians and of patients were selected and discussed in a small-group open format. The purpose of the present study was to characterize and analyze the impact of this workshop on the attitudes and clinical performances of residents.

Methods: Residents who participated in a series of poetry discussion workshops were surveyed using structured interviews designed to elicit information on the impact of the workshop on their subsequent clinical experiences and performance. Residents were encouraged to provide oral narratives of their experiences. These responses were transcribed and analyzed by qualitative methods.

Results: An impact on specific clinical decisions and on general attitudes towards patient care was demonstrated. This effect was especially seen when residents were faced with issues of communication with patients and their families, with issues of understanding the patient's perspective, and on issues of the doctor's role and responsibility. Interestingly, clinical encounters with the most severely ill patients were most likely to recall reflections of specific poems or discussions of these poems.

Conclusion: A poetry discussion workshop can have an impact on the clinical performance and attitudes of Internal Medicine residents. This impact was not dependent on the resident's cultural background or prior exposure to or interest in poetry. A poetry discussion workshop can be a useful adjunct in medical education and clinical training.

Epidemiology, Distribution and Outcome of Infective Endocarditis in Elmhurst Hospital Center, New York. F. Kandinov, M.D., Internal Medicine Resident, MSSM Elmhurst Program, and A. Lyman, M.D., MSCM, Faculty, Department of Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Aim: Infective endocarditis (IE) is a common disease entity whose occurrence and distribution is dependent on several known factors including epidemiological, behavioral (e.g., intravenous drug use), anatomical (e.g., valvular heart disease) and other predisposing conditions. The purpose of the present study was to determine the epidemiology, distribution, and outcome of patients with IE at EHC, a large ethnically diverse public hospital.

Methods: This study was a retrospective cohort design in which patients diagnosed with IE at EHC from 1/1998–12/1999 were identified from computerized database by ICD coding. The following variables were extracted by reviewing the medical record: age, gender, ethnicity, co-morbid medical conditions, IVDA status, and complications.

Results: Thirty-nine patients were identified with the diagnosis of IE during the study period; 36 charts (92%) were available for review. The patient population comprised 23 males (64%) and 13 females (36%). The most common age groups were age 41–65 years (15 patients, 42%) and 24–40 years (13 patients, 36%). By race/ethnicity, Hispanics were most prevalent (14 patients, 39%). There were 9 each (25%) of Caucasians and African-Americans, and 4(11%) Asians. Thirteen patients (36%) were known to be HIV+, while 23 patients (64%) were either HIV(–) or of unknown HIV status. Seven patients (19%) were recorded to be active intravenous drug users, and all of them (100%) were HIV+. Among the comorbid conditions that could have contributed to IE in this study, we recorded 8 patients (22%) with valvular heart disease, and 6 patients with sepsis (17%). Blood cultures were positive in 92% of patients (*S. aureus* 11 patients [31%], multiple organisms 8 patients [22%], *S. epidermidis*, *S. viridans* and *S. pneumonia* 12 patients [33%]). All patients had TTE done. Vegetations were observed in 19 patients (53%). TEE was done in 14 patients, and vegetations were found in 10 (71%). Most of the vegetations were seen on the MV (40%), AV (26%), TV (20%) or combined valve vegetations and abscesses (20%). Complications: 6 patients died of multiorgan failure [3 were in the HIV+ group and 3 in the HIV(–) group]. Surgery was required in 5 patients: 3 (23%) were in the HIV+ group and 2 (9%) in the HIV(–) group.

Conclusions: This study has described the epidemiology, distribution and outcome of patients admitted to EHC with IE. It is hoped that descriptive studies can be useful for developing strategies for reducing the prevalence or ameliorating complications of this disease.

Emergency Department High Utilizers for Exacerbation of Asthma. M.E. Brewer, B.J. Carroll, and R.A. David. Department of Ambulatory Care and Quality Management, Elmhurst Hospital Center, Elmhurst, NY.

Despite improved understanding of the pathophysiology of asthma, morbidity and mortality continue to rise, with disproportionate increases occurring among urban, indigent minorities (1).

Aim: To evaluate whether high utilizers of the Emergency Department (ED) for asthma were receiving appropriate continuity care and treatment.

Methods: We identified patients with 4 or more ED visits for asthma from 1/1/98 to 9/30/99. We determined which patients had regular clinic visits for asthma. We then attempted to contact the patients who did not use our institution for ongoing asthma care.

Results: Seventy-one patients were identified as high utilizers of the ED for asthma exacerbation. The 71 patients consisted of 39 females and 32 males ranging in age from 19–84 (mean age 40 years old). It was found that 36 (50.7%) were regularly attending clinic patients in our institution. Of the 35 (49.3%) that did not follow in our outpatient clinics, 19 (54.3%) were male and 16 (45.7%) were females; there were 18 (51.4%) Hispanics, 7 (35%) African-Americans, 6 (17%) Whites, and 4 (11.4%) Asians. The mean age was 34 for those who did not receive care here as opposed to 48 for those who did receive care at Elmhurst Hospital. None of the patients that were not followed in our institution could be contacted by letter or telephone, because of incorrect or changed telephone numbers or addresses.

Conclusion: Approximately half of the patients seen in our ED for exacerbation of asthma do receive regular and appropriate care from our Outpatient Clinics. The remainder do not receive care here on an ongoing basis. Anecdotal experience has demonstrated that undocumented immigrant status is the likely reason for our patients being unwilling to be contacted. Our findings are noteworthy with regard to the barrier to care represented by issues creating patient unwillingness to enter an ambulatory practice and instead rely on episodic ED visits, a practice known to jeopardize the prognosis of patients with asthma.

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Research by Residents: Experience of the Primary Care Internal Medicine Residency Program (PCIM), Elmhurst Hospital Center (EHC), 1992–2000. A. Lyman, MD, MSCM, MSSM Elmhurst Program, and R. David, M.D., Director, Ambulatory Care and MSSM Elmhurst Program, Elmhurst Hospital Center, Elmhurst, NY.

Residents in the PCIM are required to complete an original research project, in order to practice evidence-based medicine with an understanding of the strengths and limitations of clinical investigation and statistical inference. Residents have dedicated time in their second year to initiate their projects under the supervision of one faculty member; however, most projects are conducted during the PGY-3 year. Between academic year 1992–1993 and June 2000, 87 residents completed 87 original research projects (two residents completed 2 projects each and 2 projects were each done as a collaboration of two residents). Forty-four projects (51%) done by 45 residents (52 %) were conducted among patients or staff in the Medical Primary Care Clinic (MPC), the continuity clinic site for the residency program; 43 projects (49%) of 42 (48%) residents utilized data from other EHC settings; 10 of these used Cancer Registry data. MPC-based projects generally involved either: (a) examination of practice of MPC staff (e.g., compliance with screening or treatment protocols); (b) demographic, clinical, diagnostic spectrum, and outcome variables of patients with a particular diagnosis or clinical presentation; or (c) survey of knowledge, attitudes, beliefs, or behaviors of MPC patients or staff. One quasi-experimental clinical trial was conducted. Subject areas of non-MPC-based projects varied widely, often focusing on clinical profiles and outcome experience. 100% of projects were completed (one pending at this date). Failure to recognize the amount of time required for proper carrying-out of all phases of a research study and competing time demands of clinical duties were impedances to quality. Inadequate attention to formulation of a research question and to development of methodology were commonly observed. Sample size was usually 50–100 (although a few studies were much larger); studies were frequently inadequately powered (especially for subgroup analyses). Poor ascertainment of exposure variables due to reliance on existing clinical records and the resultant inadequate control of confounding often occurred. A further source of bias was the use of univariate analyses due to inadequate time, varying skill level, and resources available to residents for use of data entry software for multivariate analysis. Conducting research studies during residency is a difficult task, but may best facilitate assimilation of the principles of clinical epidemiology and appreciation of population medicine (1).

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Hormone Replacement Therapy (HRT) as Preventive Medicine for Breast Cancer Survivors (BCS): A Decision Analysis. H.S. Sacks, D.N. Rose, J.M. Clark, J. Lau, and D. Reitman. Mount Sinai School of Medicine, New York, NY; Long Island Jewish Medical Center, New Hyde Park, NY; Johns Hopkins University, Baltimore, MD; and New England Medical Center, Boston, MA.

Purpose: A previous decision analysis suggested that, depending on individual risk factors, HRT might increase life expectancy for many postmenopausal women, but the risks and benefits of HRT for BCS have not been studied.

Methods: We used a Markov decision analysis model for 60-year-old BCS considering HRT for preventive medicine. The outcome measure was the extension of quality-adjusted life months (QALMs) as a result of taking HRT. We used the best available information on risks of breast cancer recurrence, coronary heart disease (CHD), and osteoporosis-associated hip fractures, and the effect of HRT on these risks. We assumed that the effect of HRT found in a randomized trial of HRT for secondary prevention of CHD (the HERS study) is the same for primary prevention: an initial increase in incidence, followed by a decline. For the base case analysis, we used the median of the utility values chosen by 31 women who evaluated the pertinent health states. For the sensitivity analysis, we varied the utilities from the 25th to the 75th percentile of these values.

Results: Women at average risk for CHD and hip fracture lose 6.6 QALMs by taking HRT. Women who value the CHD and hip fracture states as having the worst impact on health and the breast cancer state as having the mildest impact on health lose the least from HRT, 5.5 QALMs. Women who value the CHD and hip fracture states as having the mildest impact on health and the breast cancer state as having the worst impact on health lose the least from HRT, 8.1 QALMs. Depending on the utility values chosen for health states and on individuals' risk factors for disease, HRT results in a loss of 1.9 QALMs (for women with a high risk for CHD and hip fracture) or a loss of 9.8 QALMs (for women with a low risk for CHD and hip fracture).

Conclusions: Unless future studies show a larger benefit on CHD mortality or other health states, HRT decisions for BCS should include careful consideration of individual preferences for all of the potential outcomes. The model can readily incorporate data on new treatments and other outcomes as they become available.

Implementing Elective Training aind Overcoming Barriers.

Tariq K. Malik, MD, MPH, and Lawrence G. Smith, MD. Mount Sinai School of Medicine, New York, NY.

Overview: The Mount Sinai Medical Center, medical house staff training program was one of the recipients of a small grant from the Partnerships for Quality Education (PQE) in 1997–1999. An $8.3 million grant program from The Pew Charitable Trusts and the Commonwealth Fund, it was an ambitious collaborative initiative to foster mutual understanding and working relationships between academic health centers and managed care.

At Mount Sinai the goal was to create an elective for a small number of residents, a unique experience which could be utilized as a model for future expansion. The sites were the corporate offices of Oxford Health Plans (a managed care organization), Manhattan Primary Care (a full risk office practice), Internal Medicine Associates (primary care continuity practice of Mount Sinai residency program) and West Side Practice (Mount Sinai's outreach practice).

Accomplishments: The experience became such a resounding success that house staff were lining up for an opening for selection. One resident chose to go into an MBA program after finishing residency.

The initiative was widely successful in many areas, in particular the development of educational materials, and trying to identify and impart the attitudes and skills needed for the trainees of the future for facing the challenges of practicing effectively and efficiently in managed care environment.

Overcoming Barriers: Being flexible and overcoming barriers was important for the success of the program. When a junior resident expressed a desire to drop out (to learn more "medicine"), it was realized that senior residents, closer to finishing training, were more suitable for selection to this training. When participating residents identified topics most relevant to them, these were included in the curriculum. When the managed care partner was experiencing financial difficulty but lacked no ardor for teaching their 'trade' (and closed major operations at the Manhattan office), our quick response was to have residents rent cars and drive to their new corporate headquarters. When an administrative error occurred it was made helpful for the financial continuation and expansion of the program beyond its anticipated age. The goodwill of the participants, in the face of odds, made the program doubly resilient.

An Innovative Elective Training in Managed Care Competencies.

Tariq Malik, MD, MPH, Lawrence Smith, MD, Michael Yedidia, Ph.D., Colleen Gillespie, Ph.D., William Suozzi, MD, Roger London, MD, MBA, and Gordon Moore, MD, MPH, Mount Sinai School of Medicine, New York, NY, New York University, New York, NY, Manhattan Primary Care, New York, Oxford Health Plans, White Plains, NY, Partnerships for Quality Education, Harvard Pilgrim Health Care and Harvard University, Boston, MA.

Objective: To implement an innovative educational experience in managed care for senior internal medicine residents. The specific focus at this institution was to initiate a pilot program that tried to impart competency in managed care for trainee residents. The larger objective was fostering mutual understanding and working relationships between academic health centers (AHC) and managed care (MC).

Design: An administrative elective was created from one of two yearly outpatient blocks of PGY3 residents. It comprised: (a) rotation at the corporate headquarters of a for-profit MC organization, (b) experience at a full risk office practice, (c) a practical introduction to setting up and managing a medical office, and (d) membership in a committee at the AHC corresponding to that of the MCO, designed to help understand health-care delivery models from different perspectives.

Results of pre- and post-training evaluation among PQE residents and comparison group (CG) were collated from a total of 56 grantee programs.

Results: (A). When perceived mastery of managed care competency in 18 topics was compared, PQE residents had better "well prepared to perform" scores in following 13 asterisked (*) topic areas versus CG group ($p<0.01$):
1. Patient Care. (Evidence Based Medicine*, Epidemiology, Cost-effective Decisions*, Population-Based*, Disease Management, Prevention, Practice Guidelines, Patient Satisfaction*, Time Management).
2. Performance Monitoring. (Utilization management, Profiling*, Continuous Quality Improvement*).
3. Teamwork and Coordination of Care. (Collaboration, Referral*, Case Management*).
4. Organizational Issues. (MC and Ethics*, MC and Health Delivery*, MC and Economics*).
(B). When attitudes about managed care were compared, PQE residents had better "strongly agree" scores of positive impacts of MC versus CG group ($p<0.01$) in the following 6 areas: Emphasize Preventive Care, Improve Continuity, Decrease Unnecessary Utilization, Increase Primary Care Physician's Role, Improve Quality of Care, Equal Access. Decrease in Health Care Cost impact was not statistically significant.

CG group had more "strongly agree" scores of negative impacts of MC versus PQE residents ($p<0.01$) in the following 4 areas: Restrict Referrals, Threaten Patient Relationship ($p<0.05$), Causes Poorer Outcomes for Sicker Patients, and Omission of Beneficial Tests.

Conclusion: An innovative program such as the one described above—with academic health centers, managed care organizations and funding agencies learning together—can be a major instrument of change.

Acknowledgment: This program was funded by Partnerships for Quality Education (PQE), an $8.3 million collaborative grant initiative from The Pew Charitable Trusts and The Commonwealth Fund.

Geriatrics

Do Cochrane Systematic Reviews Pertain to the Care of Older Adults?

Gayatri Gupta, MD, Rainier P. Soriano, MD, Jean Sullivant, MA, and Rosanne M. Leipzig, MD, PhD.

Background: Older adults infrequently participate in randomized controlled trials (RCTs), making it difficult to assess the efficacy of treatment for this population. Meta-analyses using pooled data on the older adults who do participate in high quality RCTs would provide initial data on whether older adults respond differently than younger adults. The Cochrane Collaboration is an international organization established to prepare, maintain, and provide access to systematic reviews of the effects of RCTs of healthcare interventions.

Objective: To identify the Cochrane systematic reviews relevant to the issues of older adults and to determine how age is described within these reviews.

Methods: The titles of all 657 completed reviews published in the Cochrane Database of Systematic Reviews (CSDR), Volume 4,1999, were examined by two independent reviewers for relevance to care of older adults. Irrelevant reviews, e.g., those concerning fertility or pediatric issues, were excluded.

Results: 313 reviews were identified: 174 definite and 139 possibly relevant to older adults. Several of the reviews relevant to the aged did not contain studies that included subjects over age 65, e.g., "Amantadine and Rimantadine for Preventing and Treating Influenza A in Adults." Our data suggests that: (a) the CDSR includes many topics of interest to those caring for older adults; (b) it is unusual for the number of older adults to be specified, or for there to be pooling of data by age.

Conclusion: To fulfill its mission to improve the translation of medical research into practice, the Cochrane Collaboration needs to provide users of their systematic reviews with more precise data on the ages of the subjects included in the pooled results. Additionally, it would be helpful to make available post-hoc subgroup analyses of data from older adults, particularly individual patient meta-analyses. The Cochrane Collaboration Health Care of Older Adults Field is working to institute these changes.

Assessing Differences in Symptom Burden, Care Needs and Service Utilization in Geriatric Palliative Care Patients.

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Background: Research in palliative care (PC) to date has focused on young patients with AIDS or cancer. There is no significant body of work assessing the PC needs and experiences of the geriatric population.

Objective: To determine whether PC patients over age 80 differ from younger patients in terms of symptom burden, care needs and service utilization.

Design: Retrospective data analysis of information pertaining to 1,184 first consults with the PC team of a major teaching hospital. Additionally, analysis of data derived from 755 Edmonton Symptom Assessment Scale (ESAS) forms used to measure symptom severity.

Measurements: Included patient demographics, clinical characteristics, discharge information, hospital and PC length of stay (LOS), ESAS scores, decision-making concerning advance care planning and death-prolonging treatments, and PC service recommendations and implementation.

Results: There were statistically significant differences across age groups in patient demographic and clinical characteristics, symptom burden, advance care planning and PC services recommended and implemented. Patients >80 were more likely to be women, white, widowed and Jewish. They were more likely to live in, and be discharged to, a nursing home. Age >80 was associated with a reduced prevalence of cancer as primary disease and a higher prevalence of both primary and secondary dementia. Patients >80 had shorter mean hospital LOS and hospital LOS prior to PC consult. Age >80 was associated with a lower prevalence of pain, nausea, anxiety and other symptoms, as well as lower mean ESAS scores for pain and anxiety. Patients >80 were more likely to have Do Not Resuscitate (DNR) orders. More decisions were made to withhold or withdraw five death-prolonging treatments in patients >80; there were also fewer PC interventions for symptom management in this age group.

Conclusions: A broader definition of PC may be required for those >80. PC in the geriatric population is a non-cancer model of care. It may be integrated within life-prolonging or curative treatment given the chronicity and uncertain prognoses of diseases affecting this age group. Patients >80 have compromised communication and decision-making capacity, derived in part from a high prevalence of dementia. They have a lighter symptom burden and may consume less resources per capita than younger patients. Patients >80 receive less death-prolonging treatment. Nursing home health services are especially important for those >80.
GCO# 000781

Hazards of Hospitalization: A Teaching Module for Medical Students.

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While hospitalized, the older adult is prone to develop complications unrelated to the presenting diagnosis (1). All medical students care for older hospitalized adults and therefore need to learn to recognize and prevent situations that often result in patient harm—what have been called "hazards of hospitalization" (2). MEDLINE Literature searches were conducted and articles discussing functional decline and complications during hospitalization were identified. We recently instituted a module on the "hazards of hospitalization" into our 4th year required geriatrics clerkship. Learning objectives include: describe the consequences of each hazard (e.g., bed rest, immobility, restraints, incontinence, pressure ulcers, delirium); identify age-related changes and hospital practices predisposing patients to the hazards; describe age-associated changes in pharmacokinetics and pharmacodynamics; discuss factors needing to be considered when determining a patient's hospital and discharge medication regimen; describe patient and environmental factors that need to be monitored to minimize occurrence of hazards; differentiate delirium from dementia; identify preventive measures for delirium; and describe methods of minimizing restraint use.

A series of exercises were designed for this module. Students initially write a description of an inpatient elder they cared for who suffered from "hazards" of hospitalization. They learn to differentiate delirium from dementia through bedside teaching with Acute Care for Elders (ACE) Unit patients; conduct a "hazards" patient and nurse interview and chart review; assess a medication list with respect to pharmacokinetics, dosage modification, adverse effects, drug interactions and efficacy, and discharge regimen. They are responsible for a presentation on deconditioning, aspiration, nosocomial infections, dehydration, malnutrition, or urinary catheter complications, emphasizing how aging predisposes to the condition, risk factors, prevention and treatment. At the end of the module, students review their initial patient description and discuss what might have been done to prevent complications.

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Medical Residents and End-of-Life Issues: Comfort, Skills, and Utilization of the Palliative Care Consult Service.

R.P. Soriano, D.E. Meier, H.T. Jordan, and R.M. Leipzig. Hertzberg Palliative Care Institute, Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York, NY.

Purpose: (1) To examine the housestaff's comfort and competence in dealing with end-of-life issues at the start of internship compared to their current level of training and (2) to quantitate medical housestaff's utilization of the Palliative Care Consult Service (PCCS).

Methodology: Ninety Mount Sinai internal medicine residents were asked to complete a self-administered questionnaire between September and December 1999. Surveys administered to residents utilized a retrospective before-and-after design to quantify self-assessed changes in comfort with and knowledge of end-of-life patient care. The 36-item questionnaire included closed and open-ended questions regarding self-assessed comfort with and competence in dealing with end-of-life issues, and utilization and helpfulness of the PCCS in specific areas of patient care. Two-tailed t-test was used to assess the difference in weighted means of positive responses to the questions.

Results: Fifty-four residents completed the survey (response rate=60%). There was a significant improvement in the medical residents' recall of their level of comfort in dealing with end-of-life issues at the start of internship compared with their current level of training in overall care of dying patients ($p<0.001$), management with narcotics of pain and dyspnea ($p<0.001$), management of nausea/vomiting ($p=0.002$), communication issues with patient's/caregivers regarding the dying process ($p<0.001$) and discussion of health care proxy and DNR orders ($p<0.001$). There was also a significant difference in the medical residents' perceived level of competency especially in the areas of pain and other symptom management ($p<0.001$), communication issues ($p<0.001$), and ethical issues surrounding aggressiveness of care ($p<0.001$). Notably, 14.8% (n=8) had not observed an attending interact particularly well with a dying patient. Most medical residents (81.5%) have personally requested a consult from the PCCS. The PCCS is usually consulted for pain management (63%), discussion of withdrawing or withholding life-sustaining measures (63%) and emotional/spiritual support for patient/family (51.9%). Residents have found the PCCS helpful in the areas of pain management, DNR discussions and discussions of life-sustaining measures. All of the residents who consulted the PCCS are likely to call the service in the future.

Conclusion: This study reveals that a majority of residents have utilized the PCCS and found the team helpful with end-of-life issues. They have indicated that their level of comfort and competency in dealing with palliative care issues had increased since internship. Further evaluation of data is needed to ascertain the degree to which these changes in attitudes were related to contact with the PCCS. As an educational intervention, the PCCS appears to be effective in providing competent, exemplary clinicians—role models that residents indicate are extremely effective in teaching end-of-life issues.

Acute Care for the Elderly Units: Year 2000 and Beyond. Eileen Callahan, MD, D. Thomas, MD, S. Wexler, MA, RN, CAN, H. Bloom, MD, and R. Leipzig, MD. Mount Sinai School of Medicine, New York, NY.

Acute Care for the Elderly units (ACE Units) utilize a unique physical environment and interdisciplinary approach to care for hospitalized patients at risk for functional decline and iatrogenic complications. The ACE Unit at Mount Sinai Medical Center, opened in 1996, is a 34-bed unit that provides geriatric interdisciplinary team care and serves as a major educational site for geriatric medicine and interdisciplinary team training. One thousand patients are admitted annually, 72% age 75 yrs-plus, 90% community dwelling and 75% discharged back to their homes. The average length of stay each month ranges from 7 – 9 days. Over 50% of patients are readmitted within one year of discharge, 20% of these within 14 days.

Based on these findings and our vision of the potential goals of ACE units, we have expanded upon the original descriptions of ACE units. A geriatrician and an internist-physiatrist are co-medical directors of the unit. The housestaff are core members of the interdisciplinary team, and attend daily rounds with the unit nurses, social workers, physical therapist and nutritionist to develop hospital and discharge care plans. These rounds are used as an explicit model for interdisciplinary team training, which the unit co-directors reinforce with the house staff. Attending rounds are guided by an educational curriculum of relevant journal articles and sessions on physical therapy, elder abuse and geriatric psychiatry.

Our initial results also supported a trial of a "transitional care model" as part of our ACE unit. A geriatric nurse practitioner (GNP) has been hired to attempt to decrease the rate of unplanned hospital readmissions. The GNP carefully assesses targeted patients while still hospitalized and performs home visits for up to six weeks postdischarge. Preliminary results of this effort are encouraging.

Our hospital administration views the ACE Unit as an excellent model for geriatric and interdisciplinary care and education. Ongoing goals are to decrease unplanned readmissions and length of stay, improve geriatric education, and disseminate principles of excellent interdisciplinary geriatric care throughout our medical community.

Blood Levels of Sex Hormones and Performance in Activities of Daily Living in the Nursing Home. B. Breuer[1], S. Wallenstein[2], S. Trungold[3], A. Likourezos1, C. Martucci[4], and L.S. Libow[1]. [1]The Jewish Home and Mount Sinai School of Medicine, NY, [1]Department of Biomathematics, The Mount Sinai School of Medicine, New York, NY, [1]Department of Psychiatry, The Mount Sinai School of Medicine, New York, NY, and [1]The Strang Cancer Research Laboratories , Rockefeller University, New York, NY.

Background: Interest in the relationship between sex hormones and dementia stems from the fear that age-related decrements in cognition might compromise quality of life, and the hope that hormone replacement might be beneficial. The objective of this study was to determine the relationship between dependence in activities of daily living (ADL) and blood levels of estrone (E), testosterone (T), androstenedione (A), and dehydroepiandrosterone (D).

Participants: Participants in this cross-sectional study were 370 elderly residents (mean age, 87.4 years) of the Jewish Home and Hospital, a skilled nursing facility in New York City. We measured blood levels of sex hormones and documented ADL dependency levels within 6 weeks of phlebotomy.

Results: Among the 64 male participants, dependency levels in eating and a summary ADL index were inversely related to A, E, and T (in each case, $-0.40 \leq r- \leq 0.30$ and $p<0.050$). In addition, toileting was significantly inversely related to A ($r=-0.36$, $p=0.015$), and transferring was significantly inversely related to T ($r=-0.40$, $p=0.007$). Among the 306 females, levels of E were directly related to degree of dependence for each ADL (in each case, $0.12 \leq r \leq 0.23$ and $p<0.050$), and D was significantly directly related to toileting, transferring, and the summary ADL index (in each case $0.19 \leq r \leq 0.26$ and $p<0.050$).

Conclusion: In male nursing home residents, as levels of A, E, and T increase, levels of dependence ADL decrease. Among females, however, increases in E and D are associated with greater dependence in ADL. While further studies are needed to help us understand why the nature of these relationships are so different across genders, a possible stress-related explanation will be presented.

Functions of a Geriatric Consultation Service in an Academic Medical Center in New York City. Barbara Paris, M.D., and H. Bloom, M.D. Mount Sinai Medical Center, New York, NY.

Mount Sinai Medical Center is a teaching tertiary-care hospital. The Geriatric Consultation Service is staffed by a geriatric attending, fellow, housestaff and students on a rotational basis. We provide in-hospital medical care for patients followed in our outpatient practice who are hospitalized offside our inpatient Acute Care for the Elderly (ACE) Unit. We also respond to requests for consultation throughout the hospital for patients with geriatric-related problems such as: multiple comorbidity, functional impairment, polypharmacy, dementia, delirium, falls, osteoporosis, and frailty. All new referrals to the Geriatric Practice are evaluated prior to hospital discharge, in order to more easily access information related to the hospitalization and to facilitate the discharge planning process. Another important function of the Consult Service is to provide a forum for education and clinical research for geriatric fellows, housestaff and medical students. The Ortho-Geriatric service, an interdisciplinary division of the Consult Service, has performed geriatric consultations on hip fracture patients, age 65 and over.

Distribution of Geriatric Consults between July 1998 and June 2000

	7/98–6/99		6/99–7/00	
	#	% of total	#	% of total
Referral Sources				
Geriatric Outpatient Services	130	46.0	287	64.9
Ortho-Geriatrics Unit	92	32.5	41	9.3
Teaching Service & Private Physicians	61	21.5	113	25.6
Unknown			1	0.2
Total	283		442	
Location of Patients				
Medical Unit	136	48.0	245	55.4
Surgical Unit	113	40.0	113	25.6
Specialty Unit	33	11.7	83	18.8
Unknown	1	0.3	1	0.2
Reason for Consultation by Teaching Service & Private MD's				
Transfer to Geriatrics	6	9.9	5	4.4
Patient Management	48	78.6	82	72.6
Pre-op Clearance	4	65.5	8	7.1
Discharge Planning	3	5.0	14	12.4
Other	0	0	4	3.5
Total	61		113	

Over the past 2 years, the Consult Service has increased its visibility in the hospital and enhanced its efforts to expand as a clinical teaching service, while simultaneously diminishing concentration specifically on the ortho-geriatrics unit. This has resulted in a 56% increase in the total number of patients seen in the academic year 1999–2000, compared to 1998–1999. More important, we have effected an 85% increase in our presence on teaching services throughout the hospital and requests for consultations by private physicians.

Breast Cancer Screening in Women over the Age of 70. Gretchen H. Orosz, M.D., and H. Bloom, M.D. Mount Sinai School of Medicine, New York, NY.

Background: Breast cancer occurs with increased incidence in older women, yet the efficacy of screening in women over age 70 has not been established.

Methods: A national group of clinicians, researchers and laypersons participated in a one-day working forum held in New York City. A review of the literature on breast cancer incidence, screening and treatment was presented. Included in this review were randomized trials of screening mammography, sensitivity and specificity of screening mammography and clinical breast exams (CBE), age-adjusted life expectancies, rates of screening, trends in breast cancer treatment and survival, impact of comorbidities, barriers to screening, women's treatment preferences and ethical considerations.

Results: Over the past 10 years, no major advances have been made to answer the question of breast cancer screening efficaciousness in women over age 70, and no direct evidence exists to support recommendations for or against screening. Indirect evidence, however, does lend support for screening some older women, particularly if they have no comorbidities and their life expectancy is substantial. Women who begin mammographic screening between the ages of 60 and 69 begin to show a survival benefit after 3 years, and this benefit continues for at least 12 years. In addition to the impact of screening on survival, early detection can improve quality of life and decrease morbidity. Because of the wide variability in physiologic age among women of the same chronological age, blanket screening guidelines are difficult to make for older women.

Conclusions: There is indirect evidence that some women over the age of 70 will benefit from breast cancer screening. Rather than using chronological age, the active life expectancy of women over age 70 should be used to determine whether or not they undergo screening mammography. We recommend that CBE continue in all women over age 70 and that mammography continue in women who desire screening, have no serious comorbidities and have an active life expectancy greater than 3 years. We need to make a strong commitment to continue research in this area, as the number of women over 70 is increasing dramatically.

Hematology

Involvement of Stathmin in Mitotic Progression. Sucharita J. Mistry and George F. Atweh.

Stathmin is a major microtubule destabilizing phosphoprotein that plays a critical role in the regulation of mitosis. The microtubule depolymerizing activity of stathmin is modulated by the sequential activities of specific protein kinases and phosphatases in the different phases of the cell cycle. The depolymerizing activity of stathmin is lost when it is phosphorylated. Although the importance of phosphorylation of stathmin by p34cdc2 kinase at the beginning of mitosis in the assembly of the mitotic spindle is well established, the biologic role of dephosphorylation of stathmin in the regulation of mitosis is unknown. In this study, we tested the hypothesis that dephosphorylation of stathmin may be critically important for the depolymerization of the mitotic spindle and the exit from mitosis. We compared the effects of okadaic acid, a specific inhibitor of serine/threonine protein phosphatases, on different parameters of mitotic progression in the absence and presence of relative stathmin deficiency in K562 leukemia cells. We found that inhibition of stathmin expression results in increased sensitivity to the anti-mitotic effects of okadaic acid. This was reflected by an increase in growth inhibition associated with mitotic arrest and mitotic spindle abnormalities. The stathmin-inhibited cells showed an increase in the proportion of cells blocked in a metaphase-like early mitotic stage after exposure to okadaic acid. This suggests that the loss of functional stathmin and prevention of dephosphorylation of remaining stathmin retards mitotic progression at the metaphase/anaphase transition. Furthermore, exposure to okadaic acid in the presence of stathmin deficiency results in an increase in microtubule polymerization *in vivo*. These findings suggest that dephosphorylation of stathmin is necessary for the disassembly of the mitotic spindle and exit from mitosis.

A Potential Role for Stathmin in Megakaryopoiesis. Camelia Iancu and George F. Atweh. Division of Hematology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Stathmin is a major cytosolic phosphoprotein that regulates the dynamics of microtubule polymerization and depolymerization. Maturation of megakaryocytes is associated with acquisition of markers of differentiation and polyploidization of the nucleus, both processes that require microtubule involvement. We investigated the potential role of stathmin in megakaryocytic differentiation and polyploidization. We made use of a K562 cell line in which stathmin expression was inhibited by antisense RNA expression. We compared megakaryocytic differentiation in response to 12-O-Tetradecanoylphorbol-13-acetate (TPA) in the presence or absence of stathmin inhibition. Exposure of control K562.C cells to nanomolar concentrations of TPA, a commonly used inducer of megakaryocytic differentiation, resulted in the characteristic differentiated phenotype. The cells became bigger and adhered to the plastic surface of the culture flask. They also showed loss of the erythroid phenotype as reflected by downregulation of γ-globin mRNA expression. At the same time, the cells showed a concentration-dependent upregulation of megakaryocytic markers (gpIIb, gpIIIa and B-PDGF) at the mRNA and protein level. In contrast, stathmin-inhibited K562.AS cells maintained the same size and the rounded shape and failed to attach to the plastic surface following exposure to TPA. In addition, in the presence of stathmin inhibition, K562.AS cells continued to express a weak erythroid phenotype and manifested a modest increase in the expression of gpIIb, gpIIIa and B-PDGF at the mRNA and protein levels. Thus, inhibition of stathmin expression is associated with partial inhibition of TPA-induced megakaryocytic differentiation of K562 cells. We also investigated the effect of stathmin inhibition on polyploidization that results from repeated endoreduplications and abortive mitosis in late stages of megakaryopoiesis. Upon exposure to staurosporine, an agent that induces polyploidization, a greater fraction of stathmin-inhibited K562.AS cells became polyploid with a higher degree of polyploidy compared to the control K562.C cells. Therefore, it appears that stathmin expression may be essential during the early stages of megakaryoblast differentiation. However, the later stages of megakaryocytic maturation may require suppression of stathmin expression to allow polyploidization to take place. These observations suggest that the dynamic regulation of the level of stathmin expression during megakaryocyte maturation may play an important role in their normal differentiation and polyploidization.

A Patient with Fatal Cold Hemagglutinins. Igor Genkin, M.D., and Mohamad Hussein, M.D.

Cold-agglutinin hemolytic anemia can be seen in three clinical settings: as an idiopathic disease, associated with lymphoproliferative disorders, and together with different infections. The predominant characteristic of a patient with cold hemagglutinin disease is acrocyanosis in cold, which appears reversible after warming. The clinical symptomatology of cold-agglutinin disease depends not only on a titer of cold hemagglutinins, but also and more importantly on the thermal amplitude, which is the range of temperatures over which they cause hemagglutination.

We describe a patient with fatal autoimmune hemolytic anemia due to idiopathic cold hemagglutinins.

A 47-year-old Caucasian male originally sought medical attention for jaundice, hematuria. His hemoglobin was 4.2 g/dl, LDH 2840 u/l. Remarkably, his blood already agglutinated within seconds after removal. Direct antiglobulin testing revealed antibodies against complement. Infectious disease workup including Mycoplasma assay was negative. Cold agglutinins reacted strongly with I-positive adult donor erythrocytes.

High thermal amplitude has been demonstrated. The patient was treated with warm covers, intravenous corticosteroids, and cyclophosphamide. Therapeutic plasma exchange was initiated after the condition did not improve within a few days. Despite the abovementioned measures fulminant hemolysis continued and multiorgan failure developed. The patient required artificial ventilation with inotropic support. He died a few days after admission.

It was found that the patient was using Scott's Super Turf Builder Spray (a nitrogen compound) a few days before his first symptoms began. A center for poison control did not have records of similar side effects of the compound.

Only 3 other cases of fatal cold autoimmune hemolytic anemia due to idiopathic cold hemagglutinins have been described. The causative role (if any) of this chemical remains unclear.

We are in need of new therapeutic strategies to manage cases like ours.

Safety and Efficacy of One Hour Weekly Paclitaxel Infusion and Estramustine in Hormone Refractory Prostate Cancer. Harvinder Singh, Anna C. Ferrari, Abraham Chaechoua, Mark Rosenthal, Myron Bednar, and Franco Muggia. Division of Medical Oncology, Department of Medicine; Mount Sinai School of Medicine and Division of Oncology; and New York University, New York, NY.

We conducted a trial to evaluate the MTD, toxicity and activity of a one hour weekly infusion of Paclitaxel with 3 days of high dose oral Estramustine administered in 6 weekly cycles with one week rest, in patients with hormone refractory prostate cancer. Eligible patients had a rising PSA and had failed at least two hormonal therapies. Paclitaxel was given at one of the four escalating dose levels (cohort 1–40, 2–60, 3–75, 4–90 mg/m^2). The first cohort received Estramustine at 600 mg/m2 and subsequent cohorts at 900 mg/m2 for 3 days weekly. PSA levels were obtained at wk 7 and 13. CR was defined as PSA < 4 ng/ml, PR as PSA ≤ 50%, Progression as PSA > 50% above baseline. A total of 18 patients were treated. Median age was 69. Median PSA was 287. Three patients had prior chemotherapy; 11 patients had prior RT. Cohorts 1 and 2 had 3 patients each. Cohort 3 and 4 had 6 patients each. Total number of cycles delivered was 35. All 18 patients were evaluable for toxicity and 14 patients were evaluable for response.

Toxicity: Gr.4—Pulmonary embolism (1). Gr.3—edema (1), neutropenia (1), nausea (1), diarrhea (1). Gr.2—neuropathy (1), alopecia (2), phlebitis (4), Gr.1—neuropathy (2), musculoskeletal (1), anemia (1) vomiting (2) and nausea (3).

Response: No patient achieved complete response. No partial response was observed in cohort 1. One out of 2 in cohort 2, 4 out of 5 (80%) in cohort 3 and 4 out of 4 (100%) in cohort 4 achieved partial response. Seven out of 9 patients with partial response had > 75% decline in PSA. Mean duration of response was 17.6 weeks (3–48.6).

Conclusions: Weekly Paclitaxel (75–90 mg/m^2) and 3 days of high dose Estramustine has higher activity than previously reported q3week and weekly Paclitaxel and daily Estramutine. The activity of this combination appears to be equivalent at 75–90 mg/m^2 of Paclitaxel. The toxicity of Paclitaxel is minimized by this weekly infusion schedule while the toxicity of Estramustine is constant at all doses of Paclitaxel. This combination merits further study in a larger phase II trial with emphasis on minimizing toxicity of Estramustine.

***Metachromatic Leukodystrophy (MLD) Treated with Allogeneic Bone Marrow Transplantion (BMT). A Newer Application to a Previously Lethal Disorder.** Harvinder Singh, and S. Fruchtman. Bone Marrow Transplant Service, Division of Hematology, Mount Sinai School of Medicine, New York, NY.

MLD is a lethal autosomal recessive disease, caused by the inherited deficiency of arylsulphatase A. Deficiency of this enzyme causes intralysosomal storage of the sphingolipid cerebroside sulphate: abundant in myelin. The human ASA gene is located on the long arm of chromosme 22 and encompasses about 3 kb of genomic sequence. More than 40 different mutant alleles have been characterized. Patients suffer from a progressive demyelination in both central and peripheral nervous system. It is classified according to age of onset and course of disease: late infantile, juvenile and adult types. Early onset forms advance rapidly, while a slower course is observed in late juvenile and adult forms. The disease is invariably fatal.

BMT provides a method for permanently replacing deficient enzyme activity in patients with diverse storage diseases. The rationale is based on migration of donor monocytes to the host brain. Microglia and astraglia are derived from the newly engrafted marrow. This replacement by donor cells in the brain locally corrects the recipient's enzyme deficiency. BMT has been done in rare pediatric patients with MLD. It slows or even halts the progression of the disease and stabilizes clinical, neurophysiologic and neuroradiologogic features. These favorable results occurred when transplantation was performed early in the disease. At a more advanced stage, results have been disappointing to date. There is only one published report of transplantation in an adult patient with MLD with disease stabilization at 4 years, but no improvement.

We report a 22-year-old man who underwent BMT for this disease. He is a college student who presented in 1995 with numbness of lower extremities and paraparesis. He was initially treated with plasma exchange and gamma globulins for presumed Guillian-Barre syndrome, but his neurological status deteriorated. He developed dysarthria and was wheelchair bound. EMG studies showed severe demyelinative neuropathy. MRI of the brain showed bilateral symmetric hyperintense signals within the periatrial white matter, posterior limbs of the internal capule and the middle cerebellar peduncle, suggestive of a metabolic disease. The diagnosis of MLD was confirmed by a low arylsulphatase A level in leukocytes. Considering his progressive deterioration, he was offered a BMT. He had no siblings but an HLA matched unrelated donor was identifed thru the NMDP. His conditioning regimen included cyclophosphamide and 1500 cGY of total body irradiation. He engrafted and had 99.7% gender mismatched donor mononuclear cells by day 23 on FISH analysis. He had normal leukocyte arylsulphatase A level by 3 months and an MRI done at 5 months was now normal, with resolution of earlier white matter disease. EMG studies showed improvement and his dysarthria resolved. He is now beginning to walk and undergoing rehabilitation.

This report highlights the potential of curing this lethal disorder when providing a new marrow stem cell compartment, which ultimately repopulates the dividing cells of the nervous system. A review of limited literature suggests a more positive benefit from BMT will be realized if the patient is diagnosed earlier in the course of the disease. Thus, accutate and early diagnosis of these rare enzymatic deficiencies is now crucial because corrective therapy is available. Previous reports concluded no beneficial effect of BMT if the patient had obvious neurological compromise at the time of diagnosis. Our experience indicates that this may not be true and a subgroup of patients will clearly benefit. Predictive outcomes, perhaps relating to sibling donors (potential carriers) versus unrelated donors, or questions of cell dose, require further investigation.

Gene Therapy for Pain. A.S. Beutler and M.S. Banck. Divisions of Hematology and Medical Oncology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Chronic pain is a devastating consequence of many chronic diseases and becomes the main determinant of the quality of life for many patients. Alkaloid opioids like morphine are the most effective means of pain control but cause respiratory depression, mental clouding, gastrointestinal dysfunction and other debilitating side effects. Side effects result from opioid action on the brain and peripheral organs. In an experimental study on patients, side effects could be avoided if the drug action was limited to the spinal cord (Gustafsson, L.L. & Wiesenfeld-Hallin, Z. Drugs 35, 597–603, 1988). We reasoned that gene therapy targeted to the spinal cord constituted a promising strategy for patients requiring long lasting side-effect-free pain relief.

Fibroblasts (NIH-3T3) were infected with a recombinant retrovirus encoding the cDNA of pp-EP, a fusion protein between the 121 amino acid (aa) long prepro-sequence of mouse nerve growth factor and the 31 aa long opioid peptide -endorphin (-EP). Expression of pp-EP has previously been shown to direct secretion of -EP-immunoreactive material which behaves like authentic -EP in chromatographic and immunologic analyses (Beutler, A.S. et al. J Neurochemistry 64, 475–481, 1995). $2.5\text{x}10^6$ fibroblasts secreting 2.5 ng -EP/24h *in vitro* were injected through an intrathecal catheter placed through a suboccipital incision in Harlan Sprague Dawley rats and ending in the cerebrospinal fluid filled space around the lumbar spinal cord.

Pain sensitivity of rats was assessed by recording the duration for which a rat tolerates a noxious stimulus from a hot projection bulb (vertical axis in the figure). Longer duration indicates decreased susceptibility to pain, i.e., analgesia. Testing was performed prior to injection of the fibroblasts and 1, 2, and 4 days thereafter (horizontal axis). On days 1 and 2, rats treated with pp-EP expressing fibroblasts (circles) tolerated exposure to the noxious stimulus for a longer duration than rats receiving control fibroblasts (triangles, $p<0.01$). By day 4, the analgesic effect had faded. Additional tests on the "hot plate," another pain testing paradigm, demonstrated analogous results ($p<0.05$, not shown).

Ex vivo retrovirally transduced fibroblasts were employed in these experiments as a tool to test the principle of gene therapy for pain. Adeno-associated virus (AAV) may be a promising vector to achieve a longer duration of analgesia.

The M2 Leukemia Protein AML-1/ETO Induces Cellular Proliferation by Disrupting Transcriptional Repression and Growth Suppression by the PLZF Myeloid Progenitor Transcription Factor. A. Melnick[1], G. Carlile[2], M. McConnell[2], S.W. Hiebert[3], and J.D. Licht[2]. [1]Division of Hematology and [2]Derald Ruttenberg Cancer Center, Mount Sinai School of Medicine, New York, NY; and [3]Department of Biochemistry, Vanderbilt University; Nashville, TN.

The AML-1/ETO fusion product of the t(8;21) translocation occurs in the M2 variety of acute myelogenous leukemia. This protein acts in a dominant negative manner to block the AML-1 transcription factor, required for the differentiation of hematopoietic cells. However, in addition to blocking differentiation, AML-1/ETO enhances the ability of cells to proliferate, which is not explained by its ability to repress transcription of AML-1 target genes. We previously identified the first known function of the ETO protein, which along with AML-1 contributes part of its sequence to the t(8;21) chimeric gene product. We found that ETO is a co-repressor protein for PLZF, a powerful transcriptional repressor and growth suppressor expressed in myeloid progenitor cells. We hypothesized that since AML-1/ETO retains the PLZF binding site and is present in myeloblastic (early myeloid) cells, these two proteins would interact with functional consequences for leukemia pathophysiology. We performed co-immunoprecipitations in transfected cells, and more importantly, in cells from a patient with t(8;21) AML and found that both transfected and endogenous PLZF and AML-1/ETO interact. When observed by confocal microscopy, the proteins co-localized to discrete nuclear speckles. In transcriptional reporter assays, AML-1/ETO completely abrogated the ability of PLZF to repress transcription. This effect was specific since AML-1/ETO did not affect the KRIP-1 transcriptional repressor. The mechanism of PLZF antagonism was dependent on the ability of AML-1/ETO to recruit co-repressors through the MYND-zinc finger motif of the ETO moiety, since deletion of this domain abrogated the PLZF blockade. However, sequestration of co-repressors alone could not account for the entire mechanism, since adding co-repressors in excess in transcriptional assays did not rescue PLZF. However, we also found that AML-1/ETO caused a four-fold reduction in the ability of PLZF to bind to its target genes in EMSAs. Furthermore, AML-1/ETO almost completely abrogated the ability of PLZF to associate with the nuclear matrix, which seems to be the functional compartment of this protein. Finally, and consistent with the above findings, AML-1/ETO antagonized PLZF growth suppression when co-transfected in SaOS cells. We conclude that AML-1/ETO interacts with PLZF in M2 leukemia cells, and de-represses its target genes through a complex mechanism involving exclusion from the nuclear matrix, reduction of DNA binding and interference with co-repressors, explaining at least in part the proliferative leukemic properties of these cells.

Identification of the Mechanism of Recruitment of Transcriptional Repression Machinery to Specific Target Genes by BTB/POZ proteins. A. Melnick[1], G. Carlile[2], F. Ahmac[3], G.G. Prive[3], and J.D. Licht[2]. [1]Division of Hematology and [2]Derald Ruttenberg Cancer Center, Mount Sinai School of Medicine, New York, and [3]Department of Biochemistry, Ontario Cancer Institute, Toronto, Ont, Canada.

The BTB/POZ domain is an evolutionarily conserved motif present in a number of transcription factors that regulate transcription through effects on chromatin remodeling. Several of these proteins are implicated in hematopoiesis and hematologic malignancies, including PLZF (in acute promyelocytic leukemia), Bcl-6 (in non-Hodgkin's lymphoma) and FAZF (in Fanconi's anemia). Through a crystallographic analysis of the PLZF BTB/POZ domain we found that PLZF is an obligate homodimer through the extensive interface between BTB/POZ monomers, and that dimerization is required for PLZF functions including transcriptional repression, growth suppression, high molecular weight formation and nuclear sub-localization.

In-depth mutational analysis revealed that a charged pocket region formed between the two monomers was crucial for the transcriptional effects of PLZF, independent of dimerization. To determine how the charged pocket mediates transcription repression we performed co-immunoprecipitations with both *in vitro* and *in vivo* expressed PLZF BTB/POZ domains and known PLZF co-repressor partners. We found that the charged pocket is the docking site for nuclear co-repressors and thus represents the second known structure for recruitment of chromatin remodeling machinery after the LxxLL motif of the nuclear hormone receptors. A double point mutant affecting the highly conserved (charged pocket) amino acids D35 and R49, abrogated co-repressor binding, underlining the key role of these residues in the architecture of the pocket. The same effect was seen in the context of full-length PLZF harboring the D35/R49 double mutant. In transcriptional reporter assays, the double pocket mutant was unable to cooperate with co-repressors to enhance repression. This occurred both when the BTB/POZ domain was fused to the GAL4 DNA binding domain as well as with full-length PLZF. In contrast, this mutant was a transcriptional activator, and was potentiated by the CBP and p300 transcriptional coactivators. Interestingly, the D35/R49 double mutant was able to dimerize, form high molecular weight complexes and localize to nuclear speckles the same as wild type. Thus its effect on transcription is through co-repressor interaction and not other structural effects. We conclude that we have identified a key determinant of the molecular mechanism of action of BTB/POZ transcriptional repressors. We are currently correlating these effects in Bcl-6, which has an identical pocket motif. In addition, small molecules that target this structure could have a role in the therapies of the hematologic malignancies caused by these proteins.

Adding Serum Transferrin Saturation (Tf_{Sat}) to All Routine Blood Testing Will Prevent Phenotypic Disease in Millions, Save Healthcare $Billions, and Forever End U.S. Biannual Blood Shortages: FDA Now Allows Hemochromatosis Blood to Be Used Like Any Other Donor Blood. V. Herbert and M. Spivack. Mount Sinai-NYU Health System, New York, NY and VAMC-Bronx, NY.

~12% of Americans (incl ~20% Celtic- and ~30%African-Americans) have heterozygous (H) hemochromatosis, a genotype which enhances food iron absorption. ~1% are homozygous (HH). H absorb ~50% more iron daily; HH ~300%. Genotype is diagnosed by both of 2 markers: Tf_{Sat} >42% and ferritin >200 ng/ml. Phlebotomies prevent genotype (predisposition) from becoming phenotype (disease), with insidious (slower in H [Sullivan. Circulation 100;1260–1263, 1999]) development of iron-induced multi-organ damage. FDA blanketly prohibited use of therapeutic phlebotomies as donor blood. Herbert (Am J Hemat 59(3);261–3,1998) petitioned FDA to make an exception for hemochromatosis blood. The reasons were presented at the 4/29/99 Advisory Comm. on Blood Safety and Availability, which agreed "blood products obtained from persons with hemochromatosis carry no known increased risk...the Department should...eliminate barriers to using this resource" (dhhs.gov. Search, Apr99 Adv Comm). Blood Bank Director Spivack then asked FDA for a variance to use such blood. FDA granted it 11/99, after Dr. Spivack wrote we would do the phlebotomies free (see 4/24/00 AABB Bulletin on Hemochromatosis), treat it as any other donor blood, label it in our computer as from hemochromatosis donors, and record HH donor vs other donor viral marker rates, rates of seroconversion to viral markers, post-donation reports of undisclosed risks and adverse events. Since NY State accepted in April our FDA variance, we offer free phlebotomies to H and HH genotypes.

Action: To keep the genotype millions healthy, saving healthcare$ billions, and forever end U.S. blood shortages (only 1 unit/yr from each healthy U.S. >age 17 genotype =~22 million units/yr; total current U.S. need is ~13 million units/yr), blood banks should publicize not only that they need donors, but that every healthy person, >age 17,to benefit not only others **but also** themselves, should donate a unit of blood, that they offer donors free blood iron measurement, and ~12% of Americans, most of whom don't know it, have familial high iron, and giving blood will prevent them getting insidiously progressing high-body-iron-caused tiredness, sterility, arthritis, diabetes, heart, and liver disease.

Reticulocyte γ-Globin Synthesis Predicts Responsiveness to *In Vivo* Arginine Butyrate (BU) Therapy for Sickle Cell Disease (SCD). R.S. Weinberg[1], M. Sutton[1], Y. Galperin[1], Q. Li[2], G. Atweh[1], and G. Stamatoyannopoulos[2]. [1]Department of Medicine, Division of Hematology, Mount Sinai School of Medicine, New York, NY, and [2]Division of Medical Genetics, University of Washington, Seattle, WA.

Treatment of SCD patients with BU increases HbF synthesis and ameliorates their symptoms. BU must be administered intravenously, for 3–4 consecutive days, once per month, requiring the surgical placement of a venous catheter. Increased HbF, the hallmark of BU's clinical effectiveness, is usually not evident until the patient has undergone several months of treatment. The purpose of this study was to determine if *in vivo* (reticulocyte) and/or *in vitro* (erythroid colonies, BFU-E) γ-globin synthesis, prior to and during *in vivo* BU treatment can predict responsiveness to the drug. Six patients were studied: 3 received BU alone, and 3 were treated with hydroxyurea (HU) prior to and during BU therapy. Blood was obtained from patients before treatment, and from 2 to 72 hours after the beginning of the infusions of BU. Reticulocyte γ-globin synthesis was measured by incubation of blood with ^{3}H-leucine for 2 hours, followed by electrophoresis and fluorography. *In vitro*, globin synthesis by blood BFU-E +/– BU, was examined prior to and at 24 hours during BU treatment. Five of the 6 patients responded to *in vivo* BU by increasing their levels of HbF. In all 5 responders, reticulocyte γ-globin synthesis increased 1.5 to 3-fold within 24 hours of beginning the BU infusion. One patient failed to respond to BU. At 72 hours after treatment began, his reticulocyte γ-globin synthesis was only 1%. Reticulocyte γ-globin m-RNA was assayed by RNAase protection assay pre-treatment and during BU infusions. No consistent change in γ-globin m-RNA was observed. Pre-treatment, *in vitro* BU increased γ-globin synthesis by erythroid colonies from all butyrate responsive patients, but failed to increase γ-globin synthesis by erythroid colonies from the butyrate non-responsive patient tested. In conclusion, *in vivo* BU treatment results in a rapid increase in reticulocyte γ-globin synthesis in responsive patients. Lack of commensurate changes in γ-globin m-RNA suggests that butyrate acts via post-transcriptional or translational mechanisms. We propose that comparison of reticulocyte γ-globin synthesis prior to and following 24 hours of *in vivo* BU treatment may predict responsiveness to BU therapy.
GCO# 86-245 (0001) 18 ME*

Involved Field Radiotherapy (IF-RT) and BVAC with Autologous Stem Cell Transplantation for Refractory or Relapsed NHL. T. Begaz, E. Scigliano, S. Fruchtman, B. Shank, L. Mandell, and L. Isola. Mount Sinai Medical Center, New York, NY.

Several high dose chemotherapy regimens with autologous stem cell transplant (SCT) have been shown to be effective salvage for patients with NHL in first chemosensitive relapse and second remission. Between August, 1987 and April, 1999, 71 patients with primary refractory or relapsed NHL received aggressive conditioning with BCNU 600 mg/m^2, VP16 400 mg m^2 x 4, Ara-C 3 g/m^2 x 8 and cyclophosphamide 90 mg/kg followed by autologous SCT. Patients with adenopathy ≥ 2.5 cm after optimal salvage received IF-RT (2000 cGy) to sites of bulk disease prior to SCT. Compared to other published series, our patients were a particularly poor risk group. Median age was 52 (21% > 60 years of age), 55% had primary induction failure, 7% were in remission at the time of SCT, 56% had primary refractory disease, 73% had received two or more regimens of chemotherapy prior to SCT and 84% had intermediate or high grade histology. Thirty-two (45%) patients received IF-RT. There was no significant difference in the distribution of high-risk patients and those receiving > 1 prior chemotherapy regimen between the group of patients who had IF-RT and those that did not. Median post-SCT follow-up is 699 days. Transplant-related mortality to day 100 was 25% and due to hepatic VOD or pulmonary toxicity but not influenced by age > 60. Five-year actuarial overall survival (OS) and event-free survival (EFS) were 44% ± 13% and 35% ± 13% respectively. Age > 60 adversely influenced OS (p=0.023) and EFS (p=0.006). Histology, disease status at transplant as defined by ABMTR, number of chemotherapy regimens and duration of first CR did not affect OS or EFS. Patients who received IF-RT had improved OS 49%±21% vs. 33%±17% ($p<0.015$) and marginally better EFS 39%±20% vs. 30%±15% (p=0.06). The overall relapse rate in 53 evaluable patients was 40%. The time to latest relapse was 2048 days (5.6 years). BVAC IF-RT was a highly effective conditioning regimen even in patients deemed poor candidates for autologous SCT. The toxicities of BVAC IF-RT limit its application for patients with liver and lung co-morbidities and may not justify its use in patients with good prognostic indicators, i.e., first chemosensitive relapse, low LDH and low tumor burden. Conversely, further studies using BVAC IF-RT for patients with poor transplant prognostic indicators seem warranted.

Mismatched BMT after Non-myeloablative Conditioning. L. Isola, E. Scigliano, O. Rosina, V. Najfeld, and S. Fruchtman. BMT Service, Division of Hematology, Department of Medicine, Mount Sinai Medical Center, New York, NY.

Most non-myeloablative transplantation protocols use aggressive immunosupression and G-CSF primed PBSC from HLA matched donors. We performed three mismatched transplants using unmanipulated BM after non-myeloablative conditioning and obtained rapid and complete donor engraftment. One patient had refractory NHL and the others refractory ALL and AML. One donor was a sex-matched sibling. One unrelated donor was sex-matched (female) but displayed a 9 qh+ cytogenetic polymorphism and the other was sex-mismatched (male). The related and one of the unrelated donors had a major class I mismatch at the A-locus whereas the other unrelated donor was mismatched at the DR$_1$-locus. Conditioning consisted of TBI 200 cGy, ATG, cyclosporine A (CSA) and mycophenolate mophetil (MMF). The grafts contained 6.42, 7.34 and 8.64 x 10^8 nucleated cells and 0.63, 4.68 and 5.52 $CD34^+$ cells/kg. CSA and MMF were continued in the post-transplant period. For the unrelated donor transplants, donor chimerism was assessed by cytogenetics using the 9 qh+ and Y chromosome differences. Molecular HLA typing was used in the related recipient. ANC 500 was attained on days 7 (unrelated), 11 (related) and 13 (unrelated). Platelets > 20,000 were not achieved by the related BMT patient (expired day 29). The unrelated donor recipients achieved platelet engraftment on days 17 and 18. In all three cases complete donor engraftment was documented. Within the first month post-BMT, the two patients with leukemia had no microscopic or flow cytometry evidence of disease and the NHL patient had a reduction of bulky mediastinal and abdominal adenopathy. All three patients expired with multiorgan failure and evidence of GvHD of the liver. Mismatched bone marrow transplantation can be attained without full ablation. Graft rejection was not seen in this small group of recipients with extensive previous chemotherapy. Marked response to the transplant was seen in these patients who had refractory disease. Clinically severe graft versus host disease occurred in all the patients. Although this is not unexpected, it is conceivable that the presence of persistent malignant disease or normal host hematopoiesis may contribute to GvHD by displaying class II antigens. Further refinements in conditioning and/or graft manipulation may permit mismatched transplantation without ablation.

$CD34^+$ Selection of G-CSF and GM-CSF Mobilized PBSC for Haplo-Mismatched Transplantation. L. Isola, A. Sirulnik, Y. Sinitsya, S. Richard, E. Scigliano, and S. Fruchtman. BMT Service, Division of Hematology, Department of Medicine, Mount Sinai Medical Center, New York, NY.

Recently, the use of haplo-mismatched related donors has become an alternative for patients with high-risk leukemia who do not have an HLA-identical donor. Two major obstacles to haplotransplantation are graft failure due to histocompatibility barriers and unacceptably high rates of donor T-lymphocyte mediated GVHD. The infusion of "megadoses" of $CD34^+$ cells ($>5\times10^6$ cell/kg) together with aggressive immunosuppression has proven successful in overcoming graft failure. The infusion of a T-cell (CD3) depleted stem cell product ($<5\times10^4$ $CD3^+$ cell/kg) has been shown to be critical to avoid GVHD. Stem-cell processing is needed to achieve acceptable numbers of $CD34^+$ and $CD3^-$ cells. The use of G-CSF and GM-CSF for stem cell mobilization has been shown to provide a higher $CD34^+$ and lower $CD3^+$ cell content than G-CSF alone. We describe "double cytokine" mobilization of a PBSC normal donor followed by CD34 positive selection for haplomismatched transplantation. The donor was a 3 HLA antigen mismatched sibling. Mobilization consisted of GM-CSG 5 g/kg/day days 1 – 4 and G-CSF 10 g/kg/day days 1 – 8. Collection was performed with a Fenwall CS-3000 continuous cell separator by processing three times blood volumes. Donor weight was 93 kg and recipient weight was 97 kg. The donor underwent 4 aphereses. Three cell separations were performed. Two selected products were infused and one was cryopreserved. Up to 8 x10^8 nucleated cells were loaded on an Isolex 300I device using the software version 2.5 for CD34 positive selection. Up to two collections were pooled to achieve the above-mentioned cell number. The $CD34^+$ enriched product was infused after conditioning with Thiotepa, Melphalan, Fludarabine and rabbit ATG. The cell content and phenotype for the collection and enriched product of each collection are summarized below. (Table)

Double-cytokine mobilization resulted in PBSC collections with high $CD34^+$ contents. After $CD34^+$ positive selection alone the products contained $CD3^+$ and $CD34^+$ doses that are appropriate for haplomismatched reconstitution.

TABLE
$CD34^+$ Selection

TNC PBSC Product	$CD34^+$ content PBSC product		$CD34^+$ content Positive Fraction			$CD3^+$ content PBSC Product		$CD3^+$ content Positive Fraction		
	%	Total Cells 10^6	%	Total Cells 10^6	Per kg Cells 10^6	%	Cells 10^8	%	Total Cells 10^6	Per kg Cells 10^6
80×10^9	1.32	866	96	435.6	5.0	67.8	120	0.9	0.99	0.012
80×10^9	1.12	896	96	483.8	4.5	72.2	260	0.6	0.74	0.007
69×10^9	1.9	1303	94	401.9	4.7	42.5	140	0.5	0.35	0.004

Infectious Diseases

A Diagnostic Vest against African AIDS, using Telemedicine. A Simple, Inexpensive Diagnostic Method for Determining the Incidence of AIDS and Other Medical Conditions of the General Public in Impoverished States Utilizing Telemedicine Techniques. P.C.R. Bradley-Moore, A. Bolfo, M. Saine, Noel Smith, M.D., M.D. Bradley-Moore, Prof. Melvin D. Yahr, and Ambassador V.R.W. Steward.

Mission: To provide a relatively inexpensive and discreet method of large-scale testing of a given population, to establish the condition of the heart, lungs, brain and spinal cord of each individual tested in such a manner that the data acquired can additionally be interpreted to establish the possible presence and/or stage of development of HIV/AIDS.

Concept: The person/patient will be asked to don an ordinary-looking jacket or vest, which will, however, contain a series of ultra-sensitive microphones worked into the fabric in strategic positions. An elementary keyboard and "joy stick" for measuring the patient's motor coordination will be on his lap, pedals at his feet, to record tapping. The microphones will act as a highly sensitive stethoscope and register the sounds of the heart and lungs. All information will be digitized, encrypted and instantaneously transmitted to a powerful computer at the National Institutes of Health, and there assessed and interpreted by a qualified medical practitioner standing by. The encrypted report and carrying diagnosis will be returned quickly.

Scientific Basis: Much can be learnt about a patient's well-being or sickness by listening to the sounds that his/her heart and lungs are making. The sensitivity of the microphones to be utilized will ensure that an accurate reading of those sounds can be obtained, even through clothes. Current technology enables those sounds to be captured, digitized and transmitted to a distant destination. The heart and lungs of a patient suffering from HIV/AIDS undergo a transformation which is reflected in the sounds made. Listening to these sounds enables a trained medical practitioner to determine the possible presence and/or progression of the disease in the patient.

Issues: The system, including use of the keyboard, will be designed to facilitate testing of individuals who are illiterate and will be employable regardless of their language or age.

The vest is not a threatening device and, if intelligently promoted, should cause few cultural roadblocks. As the primary results will be heart and lung oriented, no mention of AIDS need be made, maybe even at the subsequent treatment stage. The microphones will function through a layer of clothing, making the jacket acceptable to women, particularly Moslem women. No external power source is required beyond batteries. Minimal skills and training are required.

Incidence and Transmission of *Acinetobacter baumannii haemolyticus* in a NYC Teaching Hospital: 1998–1999. L.E. Finkelstein*, C. Petrec, G. Kogan, A. Moore, D. Zhang, and M.H. Mendelson. Mount Sinai Medical Center, New York, NY.

Acinetobacter baumannii haemolyticus is emerging as a significant nosocomial pathogen, primarily seen in patients who are in critical care units and/or on mechanical ventilation. An increase in the number of multiresistant *A. baumannii haemolyticus* (MDR; resistant to imipenem [I] and tobramycin [Tob] or amikacin [Ami] and an extended cephalosporin) have recently been reported. We report the results of prospective surveillance of nosocomial *Acinetobacter haemolyticus* isolates at the Mount Sinai Medical Center, a 1,100 bed (includes 78 critical care beds) acute care teaching facility located in NYC. From 1/98 – 9/99 there were a total of 278 patients identified with nosocomial *A. baumannii haemolyticus* isolates. 19 of 278 (7%) were MDR. Site distribution of 19 MDR isolates: 12 (63%) respiratory, 1 (5%) blood, 4 (21%) wound/body fluid, 2 (11%) catheter tip.

From 9/98 – 6/99 biotyping was performed on 21 (3 MDR, 18 non MDR) isolates: 9-respiratory; 3-wound 2-catheter tip; 5-blood; and 2 urine. Pulse field gel electrophoresis (PFGE) revealed 5 distinct types, 1 related type, and 6 indeterminate types. PFGE typing showed specificity and relatedness in 2 specialty areas: Cardiac Surgery, Cardiac Surgical ICU/Stepdown (Adult and Peds)/ Adult Surgical ward, 7/7 Types A/A1, 2/7 MDR. Neurosurgery: Neuroscience ICU, 2/2 Type E, 0 MDR.

In conclusion, typing of *A. baumannii haemolyticus* in 1998 – 1999 in Cardiac Surgery showed evidence of low level but continued horizontal transmission with a preponderance of non-MDR isolates during the evaluation period.

Evaluation of a Safety IV Catheter (Insyte Autoguard, Becton Dickinson) Using the Centers for Disease Control and Prevention (CDC)—National Surveillance System for Hospital Health Care Workers (NASH) Database. *MH. Mendelson, L. Chen, LE. Finkelstein, E. Bailey, and G. Kogan. Mount Sinai Medical Center, New York, NY.

A safety IV catheter (Insyte Autoguard, Becton Dickinson) was evaluated at a 1,100 bed university-affiliated medical center to determine efficacy in reducing needlestick injuries (NIs). A baseline period I (pre-safety trials) from 6/1/93 – 8/31/96 (27 months) was compared to a study period II 2/99 – 1/00 (safety IV catheter, 2 – 3/99, two-month training; 4 – 9/99, six-month pilot and 10/99 – 1/00, four-month study thus far, study ongoing). The interim between the baseline and study periods was inclusive of an evaluation of Protectiv* Plus Catheter (Johnson and Johnson). Training included model practice insertions for IV catheter users. NI data was analyzed utilizing the NaSH data collection tool and database. A survey of sharp disposal boxes was performed to assess usage and activation rates. A 94% reduction in IV stylet related NIs was demonstrated comparing the baseline period I injury rate of 6.6/100,000 IV stylets (56 injuries/848,958 IV stylets) to the study period II (12 months) injury rate of 0.4/100,000 IV stylets (1 injury/226,765 safety IV stylets) ($p<0.001$). The period II injury occurred while the stylet was being withdrawn from the patient and the HCW failed to activate the safety mechanism. A survey of 495 disposed IV stylets during the pilot period revealed 495 (100%) safety IV stylets with an activation rate of 85% (420/495). 78% of HCWs felt that the use of the safety IV catheter was very easy or easy; 76% felt there was either no change or a slight change in technique needed to use this safety device. 99% of HCWs felt that the safety IV catheter provides effective protection against needlesticks. In conclusion, the safety IV catheter (Insyte Autoguard, Becton Dickinson) resulted in a marked and significant reduction in IV stylet-related injuries during the training and pilot periods with an overall compliance with activation of 85%. Although the Insyte Autoguard requires activation by the user, the simplicity of the activation process should promote user compliance and therefore reduction in injuries. In that IV stylet-related injuries are high risk (hollow-bore) needle, inserted directly into vein or artery, if reduction of injuries continues during the study period, usage of this safety device should result in decreased blood-borne pathogen transmission to HCWs.
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Surgical Site Infections Following Laparoscopic Bowel Surgery. E. Liu, C. Petrec, J. Milsom, M. Como, A. Adebeye, G. Kogan, and M. Mendelson. Mount Sinai Hospital, New York, NY.

The Mount Sinai Hospital is a 1100 bed tertiary care hospital located in NYC; its laparoscopic bowel service performs approximately 120 surgeries per year. Laparoscopic bowel surgery (LBS) has been used for several indications including inflammatory bowel disease, colorectal malignancy, diverticular disease. The proposed benefits of LBS over conventional open surgery are faster recovery and better cosmetic results. Several studies have examined the complication rates of LBS, which appear to be comparable to those of open procedures when the former is done by experienced laparoscopic surgical teams. However, little is known about the rate of surgical site infections (SSI) from LBS.

Methods: We have retrospectively analyzed 92 cases of LBS done in 1999. We defined infections in accordance with CDC-NNIS guidelines. Infections were noted if they were deep (at or below fascia) or in organ space (below fascia).

Study Population: Forty-three patients were males, median age was 48 years. Sixteen cases were for colorectal malignancies, 43 for inflammatory bowel disease (26 for Crohn's disease, 17 for ulcerative colitis), 9 for diverticular disease.

The Standardized Infection Ratio (SIR) for laparoscopic large bowel surgeries was 1.50 (5 infections, 67 surgeries; 7.5%) with an expected number of infections of 3.33 for 67 surgeries based on NNIS data. The SIR for laparoscopic small bowel surgeries was 0 (0 infections for 18 small bowel cases; 0%) with NNIS expected rate of 1.03 for 18 cases. The overall rate of SIR was 1.15 with 5 infections per 85 cases and NNIS expected rate of 4.36 per 85 cases.

Of the 5 surgical site infections, 2 were deep and 3 were organ space. The organ space infections were polymicrobial including *E coli, Klebsiella, Serratia, and Klebsiella spp.* Three of the 5 SSIs were associated with inflammatory bowel disease and the remaining 2 surgeries were for diverticular disease and colonic dysfunction.

In conclusion, our data show SSI rates for laparoscopic bowel surgery comparable to NNIS data. Surveillance for post-operative SSIs in laparoscopic bowel surgeries is an important component of an infection control prevention program.

Prevention of Needlestick Injuries (NIs) in Healthcare Workers (HCWs): 30 Month Experience with a Resheathable "Safety" Winged Steel Needle (WSN) Using Centers for Disease Control and Prevention (CDC)—National Surveillance System for Hospital Health Care Workers (NASH) Database.

L. Chen, E. Bailey, G. Kogan, L.E. Finkelstein, and M.H. Mendelson. Mount Sinai Medical Center, New York, NY.

NIs from WSNs are considered high-risk for bloodborne pathogen transmission to HCWs. We evaluated a safety WSN (SafetyLok, BD) at a 1,100-bed hospital, previously reporting a 52% reduction in WSN related NIs by using a safety WSN. Subsequent to this trial the safety WSN was evaluated during a 19 month (6/1/98 – 12/31/99) post-study-period (total 30 months experience with this safety device). NIs were tracked using the NASH exposure form; a survey of sharps disposal boxes was performed to assess usage and activation rates. The non-safety baseline period I (9/1/95 – 3/31/97) WSN NI rate was 13.41/100,000 WSNs (86 NIs/641,282 WSNs); the study period II (7/1/97 – 5/31/98) WSN NI rate was 6.41/100,000 WSNs (28 NIs/436,180 safety WSNs); and the post-study-period III (6/1/98 – 12/31/99) WSN NI rate was 6.27/100,000 WSNs (68 NIs/1,083,071safety WSNs). The post-study WSN NI rate was 53% lower than the baseline period ($p<0.001$). Analysis of post-study safety NIs by procedure: 52 percutaneous venous puncture; 10 arterial puncture; 5 to insert a peripheral I.V. line/set up heparin lock; 1 to insert a central IV line. 37 occurred during use of item; 22 after use of item before disposal; 8 during or after disposal; 1 before use of item. 40 occurred before mechanism activation was appropriate; the safety mechanism was not activated in 13; 12 occurred during the activation process; 2 safety mechanism improperly activated. A survey of 627 disposed WSNs during period III revealed 627(100%) safety WSNs, activation rate 71% 444/627). In conclusion, the Safety Lok (BD) WSN has remained consistently effective in reducing WSN-related NIs for 30 months at our institution. Use of the Safety Lok WSN should prevent bloodborne pathogen transmission to HCWs. Compliance with proper activation procedures needs to be routinely stressed. GCO# 97-050 ME*

Access to Genotypic Resistance Testing Alters Physician Selection of Antiretroviral Therapy.

Sian Jones, M.D., and Mary E. Klotman, M.D.

The use of highly active antiretroviral therapy (HAART) has been complicated by the rapid development of antiretroviral resistance. A number of resistance assays have been developed to address this issue. We sought to determine what impact, if any, the availability of genotypic resistance testing had on the selection of antiretroviral therapy by physicians in an inner city HIV clinic. Access to genotypic resistance testing was limited to physicians whose patients were currently failing HAART for reasons other than adherence. Physicians were asked to supply information on the patients' antiretroviral history and to predict a salvage regimen at the time the genotypic assay was obtained. Charts were later abstracted to determine what effect, if any, the results of the test had on the selection of the ultimate treatment regimen. The population studied was highly antiretroviral experienced, and all patients had received at least one protease inhibitor. Of the 62 patients studied, we were unable to amplify DNA in one patient. Of the remaining 61 patients, 8 had no evidence of antiretroviral resistance, 11 had no evidence of resistance to protease inhibitors, and 23 had no resistance to non-nucleoside reverse transcriptase inhibitors. Two patients were lost to follow-up. Of the remaining 59 patients available for analysis, in 46/59 cases, access to genotypic testing resulted in a different treatment regimen than the treating physician predicted. 12/59 resulted in minor (only one change), but in 32/59 cases, significant (2 or more agents) changes were made based on the results of the genotypic testing. In 2 cases medication was discontinued entirely. In only six cases was the predicted regimen the same as that chosen after reviewing the results of resistance testing. In seven cases, after review of resistance results it was elected not to change the baseline regimen. We conclude that access to genotypic resistance testing had a significant impact on selection of treatment regimens by physicians.

SSeCKS, a Major PKC Substrate with Tumor Suppressor Activity, Regulates G1 S Progression by Controlling the Expression and Cellular Compartmentalization of Cyclin D.

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SSeCKS (Src-Suppressed C Kinase Substrate), first isolated as a G1→S inhibitor that is downregulated in src- and ras-transformed cells, encodes a major cytoskeleton- and plasma membrane-associated protein kinase C (PKC) substrate with tumor suppressor and kinase-scaffolding activities. Previous attempts at constitutive expression resulted in cell variants with truncated ectopic SSeCKS products. Here, we show that the tetracycline-regulated SSeCKS expression in NIH3T3 cells induces G1 arrest marked by extracellular stimulus-responsive kinase (ERK)-2-dependent decreases in cyclin D1 (D1) expression and pRb phosphorylation. Unexpectedly, the forced re-expression of D1 failed to rescue SSeCKS-induced G1 arrest. Confocal microscopic analysis revealed cytoplasmic co-localization of D1 with SSeCKS only when SSeCKS was overexpressed. Because SSeCKS encodes two potential cyclin-binding (CY) motifs flanking major *in vivo* PKC phosphorylation sites (Ser507/515), we addressed whether SSeCKS encodes a phosphorylation-dependent cyclin scaffolding function. Bacterially-expressed SSeCKS bound cyclins D1 and E whereas Lys→Ser mutations within either CY ablated binding. Activation of PKC *in vivo* caused a rapid translocation of D1 to the nucleus. Cell permeable, penetratin-linked peptides encoding wt SSeCKS-CY, but not [Lys→Ser] or [phospho-Ser$^{507/515}$] variants, released D1 from its cytoplasmic sequestration and induced higher saturation density in D1-overexpressor cells or rat embryo fibroblasts. Our data suggest that SSeCKS controls G1→S progression by regulating both the expression and localization of D1. These data suggest that downregulation of SSeCKS in tumor cells removes gating checkpoints for saturation density, an effect that may promote contact independence. GCO#94-055MI(A)

***Pneumocystis carinii* Pneumonia Prophylaxis with Low-Dose Atovaquone in Trimethoprim-Sulfamethoxazole (TMP-SMX) Intolerant Orthotopic Liver Transplant (OLT) Patients: A Preliminary Study.** B.R. Meyers[1], G. Papanicolaou[2], and F. Borrego[1]. Division of Infectious Diseases, Mount Sinai School of Medicine, New York, NY, and Division of Infectious Diseases, Memorial Sloan Kettering Hospital, New York, NY.

Pneumocystis carinii pneumonia (PCP) is an opportunistic infection occurring in solid organ and bone marrow transplant patients. TMP-SMX is effective in preventing PCP in these patients, but its utility is limited by high incidence of side effects, in particular bone marrow suppression and skin manifestations, both major concerns in transplant patients. This had led to consideration of alternative drugs. Atovaquone was previously shown to be effective though a higher incidence of PCP was observed with the 750 mg dose, mostly in HIV patients. This study was designed to measure efficacy and adverse effects of Atovaquone 750 mg qd in OLT patients intolerant of standard prophylaxis with TMP-SMX.

Methods: Twenty-eight patients with OLT who were started on standard PCP prophylaxis with TMP-SMX 80/400 qd had the drug withdrawn due to side effects. Patients were then given Atovaqone prophylaxis 750 QD for one year. Clinical and laboratory parameters including CBC, liver function tests and chemistries were monitored. Patients unable to receive oral medication, or those with diarrhea greater than three loose bowel movements per day x four days were excluded.

Results: Intolerance to TMP-SMX included rash in 9/28 (32%) patients; one each with Stephens Johnson syndrome and angioedema; bone marrow suppression in 13/28 (46%), diarrhea 1/28 (3.5%), and 1/28 (3.5%) elevated creatinine.

The most common side effects observed with Atovaquone were gastrointestinal (GI), 10/28 (36%), including diarrhea, bloating, taste perversion and abdominal pain. Neurologic symptoms including headache and dizziness occurred in 2/28 (7%) patients.

Four patients were discontinued from the study; 3/28 (11%) for mild to moderate diarrhea and one patient (1/28, 3.35%) for unpleasant taste.

Three patients had concomitant infections: one each *S. aureus* bacteremia, oral thrush and *C. difficile* colitis; one patient died, but this was unrelated to the study drug.

All skin manifestations (9/28, 32%) from TMP-SMX subsided. Bone marrow suppression resulting from prior therapy (13/28, 46%) improved in 62% of patients but remained suppressed in 38%, without further deterioration.

No cases of PCP occurred during the study period or thereafter for up to two years.

Conclusion: Patients intolerant to TMP-SMX generally did well on Atovaquone with GI side effects, mainly diarrhea, most commonly observed. Neither skin manifestations nor bone marrow suppression observed with TMP-SMX recurred and in 62% hemopoetic parameters improved. Four patients discontinued prophylaxis with Atovaquone, 3 with GI intolerance, 1 with taste perversion. No cases of PCP occurred in this transplant population and compliance was greatly improved by using the 750 mg QD dose. Further studies are needed to confirm these observations.

Detection of Circular Viral DNA in PBMC of HIV-Infected Individuals with No Detectable Plasma HIV RNA: Evidence for Ongoing Infection. Cara, A. Lusi, M. Keller, S. Jones, A. Mosoian, J. Vargas, A. Gurtman, A. Cohen, V. Parkas, F. Wallach, E. Chusid, and M.E. Klotman*. Division of Infectious Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

With the success of highly active antiretroviral regimens, a significant number of patients have no detectable plasma viral RNA by the most sensitive assays available. These patients, however, have persistent, replication competent virus as determined by *in vitro* culture as well as detectable viral DNA. While high levels of cc are seen in acutely infected PBMC they rapidly decline with a short half-life. Therefore, detection would be suggestive of ongoing new infection *in vivo*.

Methods: To gain a clearer understanding of the state of the virus in these patients, we examined PBMC for the presence of closed circular forms (cc) of extrachromosomal HIV DNA. Low molecular weight (LMW) DNA was specifically enriched from the cell pellet during extraction. The PCR reaction was a modification of that previously described (Cara A et al., Virology 208, 242–248) with the addition of an initial round of amplification using external primers to enhance sensitivity.

Results: DNA was extracted from the PBMC isolated from 39 patients with plasma viral loads of <50 copies HIV RNA/ml of blood. All of the patients were on multi-drug antiretroviral regimens. The mean $CD4^+$ cell count was 493 cells/mm^3 (33–984) and the mean duration of viral suppression was at least 13 months (3–27.5 mths). A total of 30 of the 39 patients or 77% of the patients had detectable cc DNA using the nested amplification. Eight of the nine patients or 89% with a detectable plasma RNA had cc2-LTR DNA, the only exception was a patient whose plasma RNA level was at the cut-off, 57. Of those patients with <50 copies of HIV RNA/ml of blood, 73% had detectable cc2-LTR DNA. In all cases, the DNA was extracted from a starting cell count of 2 x 10^6 PBMC, indicating a frequency of at least 1–2/10^6 cells containing cc2-LTR DNA in the majority of patients. There was no detectable cc2-LTR DNA in 23% of this selected patient population with sustained suppression of HIV plasma RNA.

Conclusions: While the presence of cc DNA in the majority of patients with no detectable plasma RNA suggests that there is ongoing *de novo* infection, further evaluation of the stability of this form of extrachromosomal DNA in other viral reservoirs is needed. Longitudinal studies are required to determine whether the presence of cc DNA is predictive of duration of viral suppression (or viral breakthrough).

Liver Diseases

Leptin Infusion Downregulates Long Chain Free Fatty Acid Uptake in ob/ob Mouse Adipocytes. X. Fan, M.W. Bradbury, D.D. Stump, and Paul D. Berk. Division of Liver Disease, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Administration of recombinant leptin (rL) to leptin-deficient ob/ob mice produces weight loss exceeding that attributable to reduced food intake (PNAS 93:1726, 1996). We have shown: (i) that cellular long chain free fatty acid (LCFFA) uptake consists of saturable (facilitated) and non-saturable (passive) components, and (ii) that the saturable component is up-regulated in adipocytes from ob/ob mice, diverting LCFFA toward storage as triglycerides (JBC 274:28626, 1999).

Aim: To determine whether rL infusion in ob/ob mice would lead to down-regulation of adipocyte LCFFA uptake, contributing to weight loss.

Methods: Male ob/ob mice received either rL (0.1 mg/kg/day) or PBS by continuous subcutaneous infusion for ≤21 days. Animal weight and food consumption were measured daily, and cohorts (n=3–4) were sacrificed after 0, 1, 2, 14 or

21 days of treatment. At sacrifice serum leptin and insulin levels were determined by RIA and adipocytes were isolated to measure cell surface area and [^{3}H]-oleate uptake.

Results: Data on day 0 were: weight 63.7±2.5 g (mean±SD); food intake 5.4±0.5 g; insulin 58±15 ng/ml; leptin undetectable; surface area 522±23 U^2 (1 U = 9.6μ); V_{max} for saturable oleate uptake: 32±4.8 pmol/sec/50,000 cells; and rate constant k for non-saturable oleate uptake: 0.025±0.007 ml/sec/50,000 cells. rL infusion established a serum leptin level of 32.5 ng/ml by 24 hours, with a mean of 28.9±10.9 ng/ml over 21 days. During the first 2 days, there were no changes in body weight, food intake, surface area, or k. However, insulin fell by 50 and 86% and V_{max} by 18 and 37%, respectively, after 24 and 48 hrs. All parameters fell progressively with leptin infusion. At 21 days treated animals weighed 29.9±1.4 g, food intake was 0.3±0.2 g, insulin 0.5±0.05 ng/ml, surface area 183±8 U^2, V_{max} 9.0±0.5 pmol/sec/50,000 cells, and k 0.002±0.0009 ml/sec/50,000 cells. ob/ob controls increased body weight by 4.3±2.0% over 21 days; no other parameters changed.

Conclusions: rL infusion reduces saturable LCFFA uptake and insulin by 24 hr, before detectable reductions in food intake, body weight or adipocyte size. Later decreases in non-saturable LCFFA uptake were highly correlated ($r=0.997$, $p<0.01$) with decreasing adipocyte surface area. The sequence of events suggests leptin down-regulates saturable LCFFA uptake in adipocytes either directly or indirectly (e.g., by inhibiting insulin release).

***KLF6 Induces Growth Arrest *In Vivo* by Transcriptional Upregulation of p21 Independent of p53.** G. Narla, D. Li, K. Kelley, V. Ratziu, J.H. Albrecht, F.J. Eng, and S.L. Friedman. Division of Liver Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Liver regeneration is a tightly controlled process requiring coordinated expression of both proliferative and antiproliferative signals. KLF6 (previously called "Zf9") is a ubiquitously expressed "Kruppel-like" transcription factor which is rapidly induced as an immediate early gene in hepatic stellate cells during acute liver injury.

Aims: To explore the role of KLF6 in regulating hepatic regeneration and to identify its possible transcriptional targets *in vivo*.

Methods: Transgenic mice with hepatocyte-specific expression of KLF6 were generated using the transthyretin (TTR) promoter driving a FLAG epitope-tagged KLF6 cDNA. To assess the role of KLF6 in non-hepatocytes, an NIH 3T3 cell line with tetracycline(tet)-regulated expression of KLF6 was established.

Results: Transgenic mice overexpressing hepatic KLF6 had diminished body weight, 50% less liver mass and reduced serum albumin levels as compared to wild type littermates. There was no distortion of liver architecture or inflammation, however the length of cell plates between portal triads was greatly reduced. There was no increase in cellular apoptosis as assessed by TUNEL. Importantly, the protein level of p21 (WAF1/CIP1), a potent inhibitor of several cyclin-dependent kinases and a regulator of the G1/S transition, was increased 10-fold in transgenic hepatocytes as compared to wild type littermates. In contrast, there was 80% reduction in proliferating cell nuclear antigen (PCNA) expression and 40% decrease in cell proliferation in transgenic hepatocytes as compared to wild type cells. Similarly, tet-regulated induction of KLF6 in NIH 3T3 cells led to increased p21 expression, reduced PCNA expression and a 40% decrease in cell proliferation compared to the control cells. Following transient transfection in a p53 null hepatoma cell line (Hep 3B), KLF6 transactivated a p21 promoter-reporter and also upregulated endogenous p21. Transactivation of p21 by KLF6 was unaffected by a mutation of the p53 consensus site in the p21 promoter. In p53 null mice, the pattern of KLF6 induction following partial hepatectomy was identical to the pattern of p21 induction, and was the same as in p53 wild type mice. These data suggest that p21 is a direct transcriptional target of KLF6 and that upregulation of p21 by KLF6 is independent of p53.

Conclusions: Our data reveal a unique and possibly generalized role for KLF6 in inducing p53-independent growth arrest *in vivo* by upregulating the cyclin dependent kinase inhibitor p21. KLF6 may therefore be a critical signal in regulating growth of hepatocytes.

Discoidin Domain Receptor 2 (DDR2) Interacts with Src and Shc Following Its Activation by Collagen I. Kazuo Ikeda, Calvin Lin, Elvira Olaso, Francis J. Eng, and Scott Friedman. Mount Sinai School of Medicine and Regeneron Pharmaceuticals.

Background: Receptor tyrosine kinases (RTK) play important roles in the control of cell growth, differentiation, metabolism and cell migration. Many feaures of stellate cell activation are also mediated by the induction of RTKs. Recently, our group documented the induction of DDR2, a novel RTK, during hepatic stellate cell activation. Unlike other RTKs this receptor signals in response to fibrillar collagen rather than a peptide ligand. Downstream intracellular signals mediating the effect of DDR2 have not been identified.

Aim: The present study was undertaken to identify signal transduction pathways of DDR2.

Methods and Results: We first examined whether DDR2 is phosphorylated upon binding to collagen I in immortalized rat stellate cells (HSC-T6). Following cell's stimulation with collagen I, immunopreciptation (IP) was performed on cell lysates using an antibody to DDR2 (R2-JM), followed by western blot (WB) with an antiphosphotyrosine antibody. IP-WB confirmed DDR2 expression in stellate cells, with phosphorylation occurring only after exposure to collagen I. Interestingly, Src was identified in these cell lysates in addition to DDR2, suggesting a potential role for Src kinase activity in DDR2 signaling. To identify other molecules interacting with DDR2, yeast two hybrid cloning was employed in which the cytoplasmic domain of human DDR2 was used as bait in a vector which co-expressed src-kinase domain in order to phosphorylate the receptor. A human skeletal muscle cDNA library was screened for interacting proteins following transformation in yeast. This analysis identified a cDNA encoding the CH1/ SH2 domains of the Shc adaptor protein. To confirm that Shc associates with DDR2 in mammalian cells, we used fibroblasts from DDR2-knockout mice that were reconstituted by retroviral infection with either wild type mouse DDR2 (Wt-DDR2) or a kinase dead DDR2 mutant (KD-DDR2), each stimulated with collagen I. IP-WB demonstrated that Shc associated with DDR2 only when cells expressing Wt-DDR2 were stimulated with collagen I but not in the absence of collagen. Shc association did not occur when cells expressing KD-DDR2 were stimulated with collagen I.

Conclusion: These results identify Src kinase and the adaptor protein Shc as key signaling intermediates in DDR2 signal transduction, and provide potential new targets for downregulating stellate cell activation in liver injury.

Significant Iron Overload Is Common in End-Stage Liver Disease Associated with Chronic Hepatitis B and Is Related to Nuclear HbcAg Expression. S.H. Sigal, M.D.[1], K. Ivanov, M.D.[1], M.L. Schilsky, M.D.[1], M.Carrera, RN, NP[1], A.D. Min, M.D.[1], T.D. Schiano, M.D.[1], S.L. Friedman, M.D.[1], H.C. Bodenheimer, Jr., M.D.[1], and S.N. Thung, M.D.[1]

Excessive iron deposition leads to progressive hepatic fibrosis and cirrhosis. Although hemosiderosis is a frequent finding in cirrhosis regardless of etiology, iron is the sole pathologic agent in genetic hemochromatosis. Increased hepatic iron may also exacerbate liver injury due to viral hepatitis.

Aims: 1. To evaluate the degree of hepatic iron overload in patients undergoing liver transplant (LT) for cirrhosis secondary to chronic HBV; and 2. To determine the relationship between iron deposition and hepatitis B activity.

Methods: Iron deposition (Prussian blue histochemistry), nuclear HBcAg expression (nHBcAg) and inflammatory activity were assessed in explants from patients undergoing LT for chronic HBV from 1994 to 1999. Pediatric patients and those with recent alcohol use, fulminant or subfulminant disease, portal vein thrombosis, hepatocellular carcinoma requiring pretransplant treatment, concurrent HCV or HDV infection and recent use of anti-viral therapy were excluded.

Results: The study group contained 34 patients (29 male, 5 female). Mean age was 52.8 years (range 30–71), and 10 (29.4%) were Asian. Thirteen patients had no (Grade 0), 4 mild (Grade 1), 5 moderate (Grade 2) and 12 severe (Grade 4) iron deposition. nHBcAg was detectable in 18 cases (52.9%). Thirteen (38%) livers had low (minimal or mild) inflammatory activity while 21 (62%) had marked (moderate or severe) inflammation. There was a statistical association between degree of iron overload and nHBcAg positivity (p=0.028) (see Table) that persisted after adjusting for age (p=0.059). Statistical significance between nHBcAg staining and increased inflammatory activity was borderline (p=0.064).

Summary: Significant (Grade 2+) iron overload is present in 50% of patients with end-stage liver disease due to chronic HBV, and iron deposition is associated with nHBcAg expression. These data underscore the presence of hemosiderosis in many patients with chronic HBV and emphasize the need to define its role in pathogensis.

TABLE

Parenchymal Iron Histochemical Grade	Nuclear HBcAg Expression	
	Absent (n)	Present (n)
0	9	4
1	2	2
2	2	3
4	3	9

Transcriptional Control of the Mitochondrial Aspartate Aminotransferase Gene in a Model of Alcoholic Liver Disease. M.W. Bradbury, X. Fan, and P.D. Berk. Division of Liver Disease, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Hepatic steatosis and increased serum AST/ALT ratio, with AST the mitochondrial isozyme (mAST), are hallmarks of alcoholic liver disease (ALD). In hepatocytes mAST is found on the plasma membrane (PM), where it mediates free fatty acid (FFA) uptake (Molec Cell Biochem 192: 17, 1999). Increased expression of mAST mRNA and PM mAST protein occurs during 3T3-L1 cell differentiation to adipocytes and during culture of HepG2 cells in ethanol (EtOH), a model of ALD. Both show increased FFA uptake and triglyceride accumulation, and in the latter, mAST export into medium. Thus, both markers of ALD could have one source.

Aim: To explore mechanisms underlying increased mAST mRNA in HepG2 cells in response to EtOH.

Methods: HepG2 cells were cultured for 24 h with 0–80 mM EtOH. Total RNA was isolated for Northern analysis. Cells were fractionated into mitochondria or PMs for Western blot analysis. For nuclear run-on assays, nuclei were harvested after 24 h of culture in 0 or 40 mM EtOH. RNA was isolated, labeled, and used to probe slot blots of cDNA clones. Densitometric scans determined relative levels of RNA or protein. 3T3-L1 preadipocytes and 8-day differentiated adipocytes were analyzed for mRNA levels and mitochondrial and PM mAST protein. A promoter construct containing 1.7 kb of 5' sequence and a secreted alkaline phosphatase (SEAP) reporter was transfected into HepG2 and 3T3-L1 cells. Stable clones were exposed to EtOH or differentiated, respectively, and SEAP activity measured.

Results: EtOH-treated HepG2 cells showed a dose-dependent increase in mAST mRNA. mAST protein content increased substantially only in PM. The same was seen during 3T3-L1 differentiation. HepG2 cells in 40 mM EtOH increased mAST RNA production ≥2-fold vs. controls. The promoter construct produced increased SEAP during 3T3-L1 differentiation. However, transfected HepG2 cells showed no change in activity during culture in EtOH.

Conclusions: mAST mRNA levels increase in HepG2 cells in response to EtOH and in 3T3-L1 cells during differentiation, leading to increased PM mAST protein. In HepG2 cells the increased mRNA principally reflects increased transcription. The 1.7 kb region of the mAST promoter has elements responsive to adipocyte differentiation, but not to EtOH. This research lays the foundation for uncovering EtOH-responsive elements within the mAST gene.

Medical Oncology

Synthesis of Ribozymes Targeted against Multidrug Resistance-Associated Protein (MRP) mRNA. D.P. Xu, T. Ohnuma, C.F. Qu, F-S. Wang, and J.F. Holland. Division of Medical Oncology, Samuel Bronfman Department of Medicine, Mount Sinai School of Medicine, New York, NY.

MRP is a 190-kd integral membrane protein related to P-glycoprotein (P-gp) that also confers multidrug resistance (MDR). MRP substrate drugs overlap with those of classical P-gp mediated MDR and include vinca alkaloids, anthracyclines, epipodophyllotoxins and colchicine. Physiologically MRP functions as a transporter of leukotriene C4 and glutathione. Among drug-resistant non-small cell lung cancers and colon cancers MRP1 overexpression is more often seen than classical MDR. Combined overexpression of MDR1 and MRP1 have been found in human leukemia samples. Contrary to P-gp mediated MDR, little work has been carried out to reverse MRP-related MDR.

Aims: To develop ribozymes against MRP1 mRNA and to examine their biological activities.

Methods: Two hammerhead ribozymes were synthesized, one against codon 210 and the other against codon 730 of MRP1 gene. Based on analysis of secondary structure of MRP1 mRNA by mfold 3 software the ribozymes were designed to make them accessible to their targets. MRP1 target gene fragments were obtained through RT-PCR using total RNA isolated from human laryngeal carcinoma KBv200 cells, which overexpress both MDR1 and MRP1. MRP1 gene fragments and each ribozyme were individually cloned into pGEM3Zf(-) vector. Transcription was initiated by T7 promoter in linearized recombinant vector. CT^{32}P was incorporated into substrate transcripts. Ribozyme cleavage reaction was carried out in a mimic physiological environment without denaturing RNAs. Reactive products were subjected to PAGE followed by autoradiography. To evaluate *in vivo* effect, ribozymes were cloned into adenoviral vector pCA14. Adenovirus was harvested after co-transfecting recombinant pCA14 and pJM17 into 293 cells.

Results: Sequence analysis confirmed that all constructs showed correct DNA sequences. Autoradiography data showed that both ribozymes had cleavage activity for MRP1 mRNA *in vitro*. The ribozyme against codon 210 of MRP1 gene was more efficacious than the 730 ribozyme. With molar ratio of ribozyme to substrate of 10, virtually all substrate was cleaved in 4 hours at 37°C at Mg^{2+} concentration of 5 mmol/l. Increasing Mg^{2+} concentration or reaction temperature accelerated cleavage activity. Evaluation of the effect of ribozymes in an MRP1-overexpressing cell line after adenovirus-mediated ribozyme gene transfer is in progress as is construction of a multi-ribozyme system with anti-MDR1- and anti-MRP1 ribozymes combined in tandem.

Summary: We have now developed biologically active ribozymes active against MRP1

Metaplastic Carcinoma of the Breast: A Clinicopathologic Study Based on Tumor Size. Harvinder Singh, Shabnam Jaffer, and Ira J. Bleiweiss. Division of Medical Oncology, Department of Medicine; and Department of Pathology, Mount Sinai School of Medicine, New York, NY.

Background: In contrast to conventional breast carcinoma, metaplastic breast carcinoma is usually larger (range 1 – 21 cm., mean 3.0 – 4.0 cm.), with little mention of smaller tumors (<1.0 cm.) in the literature.

Design: Based on the size of the metaplastic component, we divided 28 metaplastic carcinomas into 2 groups: ≤3.0 cm. (19 cases) and >3.0 cm (9 cases). We analyzed these cases for the following parameters: age, tumor size and grade, angiolymphatic invasion, extent of intraductal carcinoma, metaplastic component and proportion, lymph node status and hormone receptors.

Results: The age of the patients with metaplastic carcinomas ranged from 26 – 91 years (mean 62.3 years). The mean age for both the small and large metaplastic carcinomas was similar (60.8 years – small and 60.7 years – large). The size of the large metaplastic carcinomas ranged from 3.5 to 19 cm (mean = 8.0 cm) and for the small metaplastic ones from 0.7 to 3.0 cm (mean = 1.8 cm). In both categories, all carcinomas were poorly differentiated, except for one small metaplastic carcinoma that was moderately differentiated. Only 2 cases of large metaplastic carcinomas were associated with extensive high grade intraductal carcinoma, whereas most of the small metaplastic tumors (15/19) were associated with high grade intraductal carcinoma, extensive in 6 cases, with the exception of 1 case which was intermediate grade associated with the moderately differentiated duct carcinoma. Angiolymphatic invasion was similar in both small (21%) and large (22%) metaplastic carcinomas. Axillary lymph node status was available in 7 of the tumors >3.0 cm. and was positive in 6 (85.7%) cases, and available in 8 of the tumors ≤3.0 cm, only 2 (25%) of which were positive. All metaplastic carcinomas were negative for estrogen and progesterone receptors, except for the one small moderately differentiated metaplastic carcinoma. Only one large metaplastic carcinoma (4.0 cm) was positive for Her 2 Neu oncoprotein. The type of metaplastic carcinoma in both consisted of either spindle (predominant in the small carcinomas), squamous (predominant in the large carcinomas), chondroid or osteoid differentiation. A wider range was noted in the small metaplastic carcinomas from 10 – 100%, whereas in the large metaplastic carcinomas it ranged from 50 – 100%.

Conclusion: The presence of metaplasia in breast carcinoma, irrespective of amount, was associated with poor prognostic features such as higher grade of the invasive and *in situ* component, and negative hormone receptor status. Smaller metaplastic carcinomas were more frequently associated with intraductal carcinoma. In contrast, the larger metaplastic carcinomas were more likely to have metastatic carcinoma (85.7% vs 25%) to lymph nodes than the small metaplastic carcinomas.

Effects of Reovirus against Human Leukemia/Lymphoma Cells. C.F. Qu, T. Ohnuma, D.P. Xu, and J.F. Holland. Division of Medical Oncology, Samuel Bronfman Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Previous work from our laboratory showed that reovirus had cytopathic effects (CPE) against a variety of human solid tumor cell lines and that the degree of CPE correlated with the expression of Ras oncogene (Song L-T, et al. Study of reovirus-induced CPE, Ras and double-stranded RNA-activated protein kinase in human tumor cell lines. Proc Am Assoc Cancer Res 41: 350, 2000). This work suggested that reovirus may serve as an antitumor agent against human tumors with Ras overexpression. We have extended our study to include human leukemia/lymphoma cell lines.

Aims: To examine the relationship between the degree of reovirus-induced cell kill effect and the degree of Ras expression among human leukemia/lymphoma cell lines.

Methods: Human leukemia/lymphoma cell lines included MOLT-3 ALL, Jurkat ALL, HL- 60 AML, KG-1 AML, K562 CML, NCI-H929 myeloma and Daudi lymphoma cells. $5x10^3$ cells/well were inoculated in a volume of 100 ml in a 96-well plate and were infected with reovirus at the MOI of 1 or 10 PFU/cell without serum for 2 hours, followed by adding an equal volume of medium containing 20% FBS. Five days later, the viable cell number was determined using MTT assay. Ras protein was detected by Western blotting using anti-pan-Ras antibody after whole cellular proteins were extracted using lysis buffer and centrifugation.

Results: Among the cell lines tested, MOLT-3, NCI-H929 and K562 were most sensitive to reovirus infection. At the MOI of both 1 and 10, the cell kill effect reached 78 – 95%. HL-60 and Jurkat cells had intermediate sensitivities to reovirus (28 – 46%). Daudi cells were less sensitive with no cell kill at MOI of 1 and 44% at MOI of 10. KG-1 was resistant to reovirus. Ras protein detection showed that MOLT-3 had the highest Ras expression, H929, Daudi, HL-60 and Jurkat had intermediate expression. Ras expression was either weakly positive or undetectable in K562 and KG-1 cells.

Conclusion: Our results showed that in the human leukemia cell lines, sensitivity to reovirus infection generally correlated with Ras expression. Exceptions were identified in K562 cells, where cells were reovirus-sensitive even there was only weak Ras expression, and in Daudi cells, where there was lesser cell kill in spite of a moderate degree of Ras expression. While Ras-mediated signal transduction pathway appears to play an important role for reovirus sensitivity in human leukemic cells, there may be other mechanism(s) affecting the cell sensitivity to reovirus infection as demonstrated in K562 cells.

Nephrology

Relationship between Phosphorus and Creatinine Clearance in Peritoneal Dialysis: Clinical Implications. M. Sedlacek, F.D. Dimaano, and J. Uribarri. Division of Nephrology, Mount Sinai Medical Center, New York, NY.

Elevated phosphorus levels are associated with increased morbidity and mortality in dialysis patients. To study the determinants of serum phosphorus levels and phosphorus clearance we measured phosphorus concentration in 24 hr collections of dialysate and residual urine output during routine urea kinetics in 56 peritoneal dialysis patients. Dietary records were used to estimate oral phosphorus intake. The net gastrointestinal absorption of phosphorus was determined by the measured amount of phosphorus excreted in 24 hours.

The dialysate to plasma ratios of phosphorus and creatinine are very similar and the peritoneal clearances of phosphorus and creatinine correlate well and, expressed in the same units, are of the same magnitude. High transporters in the peritoneal equilibration test have higher phosphorus and creatinine clearances than low transporters. In patients who have residual urine output the renal clearances of phosphorus and creatinine are also well correlated. We compared two groups of patients with a similar KT/V≥2 but a different level of creatinine clearance, either >60 l/week or <60 l/week. The patients with the higher creatinine clearance also had a higher phosphorus clearance (7.0±2.2 versus 4.3±0.7 ml/min/$1.73m^2$) and significantly lower serum phosphorus levels (4.8±0.9 versus 5.9±1.4 mg/dl). The daily amount of phosphorus absorption was actually higher (490±190 versus 336±100 mg/day) in the patients who had greater phosphorus clearance and lower phosphorus levels. The oral intake of protein and phosphorus are closely correlated (r=0.754, p<0.0001).

In summary, creatinine clearance and phosphorus clearance are closely linked in peritoneal dialysis. Patients with a limited amount of creatinine clearance can tolerate only limited amounts of dietary phosphorus and hence dietary protein without having a rise in their serum phosphorus level. These data may be of help in the current controversy about which amount of daily protein intake should be recommended to peritoneal dialysis patients.

AAV Mediated Expression of Insulin in Renal Epithelial Cells. M. Sedlacek, L.A. Bruggeman, K. Zhao, R.M. Linden, S.L.C. Woo, and P.E. Klotman. Division of Nephrology and the Institute for Gene Therapy, Mount Sinai Medical Center, New York, NY.

The restoration of a permanent and regulated source of insulin by gene therapy would be a significant improvement in the treatment of diabetes mellitus. As the kidney is anatomically well suited as a production site for insulin we explored the feasibility of using this organ as a target site for insulin gene therapy.

Rat I insulin gene was mutated to allow for processing by ubiquitous furin proteases and to facilitate detection by the FLAG tagging system. The expression of rat insulin from this gene was tested by radioimmunoassay in available renal cell lines. The highest levels of insulin were obtained with the EF-1 promoter. Proinsulin was detected by western blotting with anti-FLAG antibody if the transfected gene contained the FLAG mutation and with anti rat C-peptide antibody if the gene did not contain the FLAG mutation. The secretion of a proportion of the insulin towards the basal (bloodstream) compartment was tested in the MDCK transwell model of polarized renal epithelium.

Recombinant adeno-associated virus (rAAV) was produced containing the modified rat I insulin gene. 2×10^{11} viral particles were injected into the renal pelvis of one kidney each of two anesthetized mice. Insulin could be detected in isolated medullary tubules by immunohistochemistry using anti porcine insulin antibody. Approximately 1×10^{11} rAAV were used to infect polarized MDCK cells from either the apical or the basal side (6 transwells each). MDCK cells infected from the basal side produced much more insulin than MDCK cells infected from the apical side. Most of the insulin was secreted toward the basal compartment.

In summary, renal epithelial cells can produce RIA detectable insulin and a large proportion of that insulin is secreted towards the basal (bloodstream) compartment. Insulin expression can be induced *in vivo* in mouse kidney using rAAV as a vector. Polarized renal epithelial cells infected with rAAV from the basal side produced much more insulin than when the infection occurred from the apical side. The kidney is a feasible site for insulin gene expression but more efficient methods of gene delivery are required.

Hemodialysis Access Placement with Preoperative Noninvasive Vascular Mapping: Comparison between Diabetic and Non-diabetic Patients. M. Sedlacek, V. Teodorescu, A. Falk, J. Vassalotti, and J. Uribarri. Division of Nephrology, Department of Interventional Nephrology and the Department of Vascular Surgery, Mount Sinai Medical Center, New York, NY.

Diabetes mellitus is the leading cause of end stage renal disease (ESRD). Compounding the cost of diabetic ESRD to Medicare is the common belief among physicians that diabetic patients are poor candidates to have fistulae placed as dialysis access. As there are no data supporting this viewpoint, we retrospectively compared the results of preoperative vascular mapping by Duplex ultrasound and subsequent surgical vascular access placement in patients who have either type I or II diabetes and non-diabetic patients.

There was no difference in venous size between 81 diabetic and 108 non-diabetic patients. There was also no difference in radial and ulnar peak systolic velocity measurements between diabetic and non-diabetic patients. 110 patients had vascular access surgery performed and hemodialysis had been started in 105 of these. There was no difference between the proportion of diabetic (67%) and non-diabetic patients (63%) who had a fistula placed as dialysis access (X^2=2.7, df=2, p=0.26, NS). There also was no difference in the percentage of these fistulas that were in use as the sole dialysis access between diabetic (71%) and non-diabetic patients (86%) (X^2=0.18, df=1, p=0.18, NS). The percentage of patients who had dialysis using a temporary catheter was not different between diabetic and non-diabetic patients (18% versus 14%, X^2=0.8, df=1, p=0.37, NS).

In summary, contrary to conventional wisdom, the results of our data on vascular access in hemodialysis patients show no significant difference between diabetic and non-diabetic patients in terms of venous and arterial anatomy, prevalence of fistula placement, percentage of functioning fistulae and percentage of patients dialysed with a catheter. Additional studies are required to determine the long-term outcome of AV fistulae in diabetic patients.

Midkine Stimulates Expansion of the Renal Progenitor Cell Compartment and Inhibits Nephrogenesis in Metanephric Organ Culture. L. Qiu, D. Hyink, K. Amsler, P.D. Wilson, and C.R. Burrow. Division of Nephrology, Mount Sinai School of Medicine, New York, NY.

The control mechanisms which regulate progenitor cell growth in the metanephroi are important determinants of nephron number in the adult kidney. Recently, FGF-2, BMP-7, and an unidentified factor or factors secreted by the stromal cell compartment have been identified as signals which promote the proliferation, survival or differentiation of undifferentiated renal progenitor cells in the metanephric kidney. Since we have previously found that G401 conditioned media, which contains FGF-2, BMP-7 and midkine (MK), is mitogenic for metanephric blastemal cells *in vitro* (PNAS 90 :6066–6070, 1993), and shown that MK stimulates G401 cell proliferation (JBC 273:3654–3660, 1998; Qiu et al. Biochemistry 39:5977–5987, 2000), we analyzed the effects of this growth factor on nephrogenesis in cultured metanephroi. For these studies, E12.5 mouse metanephroi were cultured in the presence or absence of highly purified recombinant MK in serum-free media and its effects on kidney development analyzed. MK treatment (7 nM for 5 days) produced the appearance of large masses of undifferentiated blastemal cells in the subcapsular region which surrounded the ureteric bud ampullae. In these regions, nephron Anlagen including vesicles, comma-shaped and S-shaped bodies were absent. Quantitative studies showed that MK-treated metanephroi had reduced ureteric bud branching [after 2 days in culture, number of branches: 16.4±1.5 (MK) versus 28.0±2.6 (control), $p<0.05$] and reduced formation of glomeruli [after 5 days, number of glomeruli: 39.6 ± 8.0 (MK) vs 61.0 ± 9.2 (control), $p<0.05$] but no effect on overall organ growth in culture was found by analyzing organ size or protein content at 5 days [μg protein/kidney 29.9±2.3 (MK) vs 31.8±2.9 (control), $p>0.05$]. These results suggest that MK may play an important role in the regulation of renal progenitor cell number either as a survival factor, by blocking progenitor cell proliferation, or by acting as an autocrine growth factor during kidney development.
GCO# 97-469

Prevalence of AV Fistulas at the Bronx VA Medical Center Dialysis Unit. C. He, V. Charoenkul, T. Kahn, E. Langhoff, J. Uribarri, and M. Sedlacek. Division of Nephrology and Department of Surgery, Bronx VA Medical Center, Bronx, NY and Division of Nephrology, Mount Sinai School of Medicine, New York, NY.

A decreased use of native AV fistulas and an increased use of synthetic grafts as permanent dialysis access have accompanied the growth of the dialysis population in the United States. It is well known that AV fistulas have superior 5-year patency rates and fewer complications than other types of access. Several patient-related factors have been blamed to explain the trend toward synthetic grafts, such as the presence of vascular disease, diabetes mellitus, age and comorbidities. In a cross-sectional analysis we describe these factors and determine the prevalence of AV fistulas in our dialysis population at the Bronx VA Medical Center.

There are 51 chronic hemodialysis patients with an average age of 66 years. 59% are African American, 24% white and 10% Hispanic. 29 of 51 patients (57%) are diabetic and almost everybody has a history of hypertension. 18 patients (35%) had amputations or arterial bypass surgery, 19 patients (37%) have documented coronary artery disease and 6 patients (12%) suffered a stroke. 18 patients (35%) are active smokers and 11 patients (22%) have a history of intravenous drug use. All patients had their dialysis access placed by the same surgeon. 38 of 51 patients (75%) use an AV fistula as primary dialysis access, 9 patients (18%) are dialyzed through a catheter and 4 patients (8%) use a synthetic graft. 4 of the 9 patients who are dialyzed through a catheter have a maturing fistula, thus increasing the prevalence of AV fistulas to 82%. 9 of the 38 patients with a fistula use their access for more than 5 years and 5 of these 9 patients are diabetic.

In conclusion, 75% of the chronic dialysis patients at the Bronx VA Medical Center are dialyzed through an AV fistula, which compares well with the 33% prevalence at the national level. The Bronx VA dialysis patients are neither distinguished by compliance nor privileged by health. We believe that our example shows that the presence of a skilled and dedicated surgeon is more predictive of better dialysis access than other factors.

Cyclic AMP-Dependent Regulation of Polycystin-1 Phosphorylation, Signal Transduction and Transcription by Protein Kinase (PRKX). Xiaohong Li, Christopher R. Burrow, Hsi-Ping Li, and Patricia D. Wilson. Department of Medicine, Division of Nephrology, Mount Sinai School of Medicine, New York, NY.

The PKD1-encoded protein, polycystin-1, is a modular membrane protein with extracellular ligand binding motifs, 11 transmembrane (TM) domains and an intracellular C-terminal portion with several putative phosphorylation and proline-rich sites typical of signaling molecules. Our previous studies showed that PKD1-CTD fusion protein is phosphorylated by PKA at S4252 in an RRSSR consensus (Li, BBRC 1999). We have now identified by cloning and sequence analysis, that PRKX, a serine/threonine kinase is restricted in its expression to fetal (HFK) and ADPKD kidneys, but absent from normal human adult (NH) kidneys, as determined by Northern analysis and *in situ* hybridization. PRKX is co-expressed with polycystin-1 in ureteric bud epithelium of HFK and in ADPKD cyst epithelia. We also show that PRKX can phosphorylate PKD1-CTD, in a cAMP-dependent manner, by incubation of purified His/FLAG PKD1-CTD fusion protein with lysates prepared from PRKX-transfected, PKA-deficient JAR cells. Transfection of PRKX/GFP into LLC-PK1 cells showed that, like PKA, PRKX translocated to the nucleus after cell treatment with 8Br-cAMP. PRKX stimulated cAMP-responsive (CRE)-luciferase reporter gene transcription identifying it as a CREB/ATF kinase. Since cAMP-dependent protein kinases and PKD1 can cooperatively activate AP-1 dependent gene expression, cAMP and PRKX may be important modifiers of abnormal gene transcription in ADPKD.

Pulmonary

Non-compliance with Prescribed Therapy as a Predictor of Recurrent Hospitalizations and Emergency Room (ER) Visits in Patients with Severe Asthma. W. El-Halees, M.D., R. Theerthakarai, M.D., and M.A. Khan, M.D. St. Joseph's Hospital and Medical Center, Paterson, NJ, and Seton Hall University, School of Graduate Medical Education, South Orange, NJ.

Introduction: Despite unprecedented advances in the management of bronchial asthma, frequency of hospitalizations and ER visits by the asthmatic have not declined. This study explores the role of non-compliance with prescribed treatment in the exacerbations of asthma in an inner-city group.

Methods: We evaluated 43 patients (18 m, 25 f; mean age: 41 years) hospitalized for an acute exacerbation of asthma over a six-month period. All patients had severe asthma with continuous symptoms and peak flow rates $< 60\%$ predicted. Eleven (26%) patients had status asthmaticus and 7 required mechanical ventilation. Each patient underwent a detailed interview to assess compliance with therapy, ER visits and hospitalizations during the past one year.

Results: Fourteen of 43 (33%) patients were categorized as non-compliant with therapy while 29 (67%) were considered to be compliant. Non-compliant patients had more frequent (mean: 4.9) E.R. visits compared with those in the compliant group (mean: 2.3; $p<0.005$). Similarly, patients in the non-compliant group had more frequent (mean: 3.2) hospitalizations compared with those in the compliant group (mean: 1.5; $p<0.001$).

Conclusion: Non-compliance with treatment is a significant predictor of frequent hospitalizations and ER visits in an inner-city group with severe asthma.

The Role of Recent *Mycoplasma pneumoniae* Infection in Acute Exacerbation of Bronchial Asthma. W. El-Halees, M.D. R. Theerthakarai, M.D., R. Solis, M.D., and M.A. Khan, M.D. St. Joseph's Hospital and Medical Center, Paterson, NJ and Seton Hall University, School of Graduate Medical Education, South Orange, NJ.

Introduction: The role of infection with *Mycoplasma pneumoniae* in the exacerbation of bronchial asthma remains controversial. In this prospective study, we investigated the effect of a recent infection with *M. pneumoniae* on patients with bronchial asthma who were hospitalized with an acute exacerbation.

Methods: We prospectively evaluated 14 patients (6 males, 8 females, mean age: 43 years) who were hospitalized with an acute exacerbation of bronchial asthma. All patients had severe bronchial asthma; (FEV$_1$ $< 60\%$ predicted); 6 patients had status asthmaticus and 4 patients required mechanical ventilation. All patients had a negative chest x-ray on admission. The control group consisted of 15 patients (7 males, 8 females; mean age 48 years) who had no history of asthma and none had pneumonia during the past 5 years. Mycoplasma titers were obtained on all patients and controls. Patients with mycoplasma IgG titer > 340 U/ml or positive IgM titers were considered to have active mycoplasma infection.

Results: Four (29%) patients with bronchial asthma had active mycoplasma infection (4 with IgG > 340 U/ml and one with IgM as well). Only one subject (7%) in the control group had IgG >340. (p value < 0.001).

Conclusion: Recent infection with *M. pneumoniae* is a significant cause of acute exacerbation of bronchial asthma.

A Comparison of Roentgenographic Findings between Pulmonary Tuberculosis (TB) and Mycobacterium Avium Complex (MAC) in AIDS Disease. S. Javadpoor, M.D., R. Theerthakarai, M.D., and M.A. Khan, M.D. St. Joseph's Hospital and Medical Center, Paterson, NJ and Seton Hall University, School of Graduate Medical Education, South Orange, NJ.

Introduction: The roentgenographic presentation of pulmonary MAC is variable. In order to differentiate TB from pulmonary MAC, on the basis of initial chest roentgenogram, we retrospectively reviewed our experience in an inner-city clinic.

Methods: We retrospectively reviewed the records and chest roentgenograms of 31 AIDS patients from January 1997 to December 1998. Patients were divided into 2 groups; Group 1: culture positive TB; Group 2: culture positive MAC. These two groups were compared with a control group # 3: TB without HIV (36 patients).

Results: Results of the initial chest roentgenographic presentation are as follows:

Conclusions: Diffuse disease is a frequent finding in AIDS with TB while a normal chest film is frequent in AIDS with MAC.

	Upper lobe infiltrate/ Lower lobe infiltrate	Bilat diffuse infiltrate	Hilar nodes/ Pleural effusion	Cavitary lesion	Normal
Group 1	2 (20%)/1 (10%)	5 (50%)	1 (10%)/3 (8%)	1 (10%)	0 (0%)
Group 2	5 (24%)/3 (14%)	6 (29%)	0 (0%)/0 (0%)	0 (0%)	7 (33%)
Group 3	15(44%)/5(14%)	6 (17%)	1 (3%)/3 (8%)	5 (14%)	0 (0%)

Significance of Pulmonary Function Changes after Bone Marrow Transplantation (BMT) in Predicting Mortality. R. Theerthakarai, M.D. S. Javadpoor, M.D., C. Anselmi, M.D., and M.A. Khan, M.D. St. Joseph's Hospital and Medical Center, Paterson, NJ and Seton Hall University, School of Graduate Medical Education, South Orange, NJ.

Introduction: The effect of BMT on pulmonary function and its predictability for mortality vary in different studies. To evaluate the effect of BMT on pulmonary function, we retrospectively reviewed our data from December 1993 through January 1999.

Methods: A total of 65 patients underwent BMT, of whom 28 (15 males, 13 females, age range 12–68 years; mean age: 42 years) had undergone pulmonary function studies before and after BMT. Pulmonary function changes before and after BMT were classified as restrictive (TLC < 80% of predicted) or as obstructive (≥ 5% decline in FEV1/FVC from baseline).

Results: Out of 28 patients, 6 (21%) showed restrictive pattern and 8 (29%) showed obstructive pattern. Fifteen-month mortality rate was 83% (5 of 6 patients) in restrictive group and 38% (3 of 8 patients) in obstructive group ($p<0.132$).

Conclusions: Our study shows that the post-BMT obstructive pattern is more frequent than the restrictive pattern and that the restrictive pattern is associated with an increased mortality.

Improvement in Pulmonary Physiology after Paraesophageal Hernia Repair in Patients with Dyspnea and Restrictive Lung Dysfunction. A. Garrow, and A.S.Teirstein. Mount Sinai School of Medicine, New York, NY.

Introduction: Type II- IV paraesophageal hernias are associated with migration of the stomach and other intraabdominal viscera through the diaphragmatic hiatus into the mediastinum. In patients with underlying restrictive ventilatory defects due to kyphosis, obesity, or chest wall deformities, the space occupying effects caused by the hernia contents can add significant respiratory dysfunction in addition to the known complications of chronic anemia and gastric volvulus with necrosis. In the past many of these patients have been considered too great a surgical risk to withstand a laparotomy or thoracotomy for paraesophageal hernia repair. During the last decade laparoscopic paraesophageal hernia repair has been shown to have better results, shorter hospital stays and decreased morbidity compared to open repair. The purpose of this study is to document improvement in dyspnea and pulmonary function with the laparoscopic correction of paraesophageal hernias.

Methods: An ongoing study evaluating the pulmonary physiology of patients with paraesophageal hernias and underlying restrictive lung disease by preoperative and postoperative pulmonary function tests. (Table)

Results: Nine patients underwent hernia repair. Preoperative spirometry revealed restriction in 4/9. Spirometry revealed a combined restriction and obstruction in one. One patient had an obstructive airflow pattern. Three patients had spirometry that was within normal limits for their age, sex and weight. Postoperative pulmonary function tests were performed. All patients reviewed had some improvement in their spirometry.

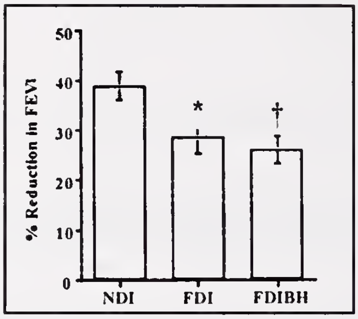
Table
Improvement in pulmonary physiology after para-esophageal hernia repair

Patient	Preop FVC (%Pred)/ TLC (%Pred)	Postop FVC (%Pred) /TLC (%Pred)	Percent change*
A	1.60 (53%)	2.50 (71%)	56%
B	1.22 (49%)	1.77 (71%) / 3.54 (85%)	45%
C	1.48 (63%)	1.74 (71%)	18%
D	1.74 (65%)	2.01 (75%)	15%
E	1.72 (54%)	1.98 (61%)	15%
F	2.80 (86%) / 4.17 (84%)	2.68 (83%) / 4.58 (93%)	10%
G	2.00 (68%)	2.18 (80%)	9.0%
H	2.24 (76%) / 4.23 (88%)	2.15 (75%) / 4.51 (94%)	6.6%
I	2.47 (82%)	2.62 (91%)**	6.1%

Conclusion: Paraesophageal hernia repair may significantly improve patients' restrictive ventilatory defects and pulmonary symptoms. The use of laparoscopic technique has decreased the morbidity of this surgical repair, and made it a reasonable option in patients who may not tolerate laparotomy and/or thoracotomy for repair of their paraesophageal hernia.

The Influence of Breath Holding on the Bronchoprotective Effect of Fast Deep Inspiration. D.N. Jourdy, E.N. Schachter, and G.S. Skloot. Division of Pulmonary and Critical Care Medicine, Mount Sinai School of Medicine, New York, NY.

We have previously shown that the ability of a deep inspiration (DI) to protect against Methacholine (Mch)-induced bronchoconstriction in healthy subjects (HS) depends upon inspiratory flow; a fast (F) DI was bronchoprotective while a slow DI was not (AJRCCM, 1999; 159(3):A468). A possible mechanism in HS is that an FDI stretches airway smooth muscle and breaks cross bridges. We hypothesized that in HS the effect of an FDI is related to the duration of inspiration, i.e., an FDI with a breath hold (BH) at TLC prior to passive exhalation is more bronchoprotective than an FDI without a BH. We studied 11 HS (mean FEV_1 % pred±SEM = 97±3), screened on day 1 by routine Mch challenge (PC20>75 mg/ml). On day 2, subjects performed 3 FVC efforts and then underwent modified Mch challenge with no DIs (NDI); only partial forced expirations were done after each dose. The threshold dose (DT), defined by symptoms and/or partial $FEV_1/FVC \le 0.55$, was followed by 3 FVC efforts. A ≥20% reduction in FEV_1 from baseline was a prerequisite for further study. On days 3 and 4, the protocol was identical to day 2 except that immediately prior to DT, subjects took either an FDI or an FDIBH [mean maximal inspiratory flow (L/s) 4.97 vs. 5.01, p=NS; mean inspired volume (L) 2.55 vs. 2.45, p=NS]. The mean % reduction in FEV_1 post-DT (compared to baseline) on days 2–4 is shown in the figure. A significant difference was seen for both FDI vs. NDI (*p=0.019) and FDIBH vs. NDI (†p=0.005). However, there was no significant difference for FDI vs. FDIBH (p=0.556). These results suggest that prolonging the duration of a fast DI with a BH does not enhance bronchoprotection in healthy subjects. We speculate that breath holding at the end of a fast DI does not lead to additional cross bridge breakage or sliding of visco-elastic elements.



GCO# 96-611 (0002) 04 ME*

The Effect of Repeated Antigen Challenge on Airway Smooth Muscle Stretch Induced Relaxation. A. Gadgil, G.S. Skloot, N. Rienzi, S. Liang, and E.N. Schachter. Mount Sinai School of Medicine, New York, NY.

We have previously studied the response of stretch-induced relaxation (SIR) in guinea pig (GP) trachea evaluating the role of mediators (AJRCCM 1998; 157:A515), and of allergic inflammation induced by a single ovalbumin (OA) challenge (AJRCCM 1999; 159:A469). We compared SIR in tissues from multiply (M) and singly (S) challenged GPs. GPs were sensitized using 3 successive intraperitoneal injections of OA given over one week. The S challenged GPs received an aerosol of 2.5% OA on day 21. The M challenged GPs were challenged on days 21, 24 and 27. A control group of unsensitized GPs received sham challenges of double distilled water. Animals were sacrificed 24 hours after the final challenge. GP tracheal rings were suspended in physiologic buffer and maintained at baseline tension of 2 g. Individual rings were stretched by applying tensions of 2.5, 5, 10 or 15 g. After equilibration, tissues were washed and reset to 2 g. Carbachol (10-4 M) was added and maximal constriction measured. The response to stretch was again studied. We compared the responses in 13 M challenged GPs to those in 18 S challenged GPs. The inflammatory response in sensitized animals was confirmed histologically by the presence of infiltration of eosinophils into the mucosal epithelium. Control animals demonstrated significantly greater SIR post-carbachol than pre-carbachol. In S challenged animals this accentuation by carbachol was considerably dampened. In M challenged animals, the accentuation by carbachol was once again seen (similar to controls). There was a trend toward a greater carbachol response in M challenged GPs compared to those S challenged. This latter observation may explain the increased SIR response following carbachol in M challenged GPs. Alternatively the M challenged animals may have experienced tachyphylaxis to the multiple OA challenges and thereby returned to the baseline (control) state. These data suggest that the SIR response is different in GPs M challenged with OA compared with those S challenged.
Catherine and Henry J. Gaisman Foundation, NY.
GCO# 88-250ME

Cellular Immune Response Is an Independent Predictor of Mortality in Chronically Critically Ill Patients. T.H. Kalb MD, N. Goldstein MD, A. Garrow MD, E. Sapira MS, J.I. Mechanick MD, and D.M. Nierman MD. Division of Pulmonary/Critical Care Medicine, Division of Clinical Immunology and Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Background: The term chronic critical illness (CCI) has been coined to describe patients who do not wean within two weeks of critical care and require tracheotomy. We have previously described that cellular immune dysfunction is prevalent in a small cohort of chronically critically ill (CCI) patients. Immune function impairment as measured by an *in vitro* lymphocyte stimulation assay (LSA) to candida antigen was correlated with mortality (p=0.015 by Fisher Exact Test) and weaning success (p=0.02).

Hypothesis: In the present study we hypothesized that this assay of immune function was an independent marker of outcome in CCI patients. To test this hypothesis, we sought to determine whether or not LSA testing results were statistically associated with simple clinical or demographic features of CCI patients.

Method: Retrospective chart review for the purpose of multivariate analysis was conducted for all CCI subjects who had undergone LSA assay (n=22). Correlations were sought between LSA response and clinical variables selected laboratory values on the day of LSA assay. Continuous variables were analyzed using Pearson's correlation coefficient. Noncontinuous variables were analyzed using Kolmogorov-Smirnov Test. Variables were chosen because of their reported influence on immune function (e.g., advanced age, cancer) or on nosocomial acquisition of candida (e.g., prior antibiotic use, tracheostomy duration).

Results: No correlation was found between LSA value (in SI units) and clinical variables including age, gender, underlying co-morbidities (cancer, diabetes mellitus, renal insufficiency), prior infection and antibiotic use during hospitalization, duration of hospital stay prior to RCU transfer, duration of tracheostomy and central venous catheterization, presence of percutaneous gastrostomy tube, and prior use of parenteral nutrition, glutamine supplementation, nor to selected laboratory values on the day of LSA assay (WBC, lymphocyte count, percent lymphocyte count, serum albumin and pre-albumin).

Conclusion: Clinical variables gleaned from chart review did not predict immune dysfunction by LSA testing. Therefore, LSA testing may prospectively and independently identify those CCI patients who are at increased risk for mortality. GCO# 97-0530ME* (00001)

Rheumatology

Dialysis Amyloidosis (DA): Clinical, Radiologic and Biochemical Features. Qing Guo, James Ripellino, George Hermann, Michael Klein, and Peter D. Gorevic. Departments of Radiology, Pathology and Medicine, Mount Sinai School of Medicine, New York, NY.

DA is a major morbidity among patients being managed by long-term hemodialysis or chronic ambulatory peritoneal dialysis; clinical manifestations include entrapment neuropathy, osteoarthropathy, destructive cystic bone disease, spondyloarthropathy and, in a small percent of cases, systemic amyloid deposition. More than 200,000 patients undergo dialysis currently in the United States, and it is estimated that this number will rise to over 350,000 by the year 2010. DA continues to be a morbidity among the 70,000 patients who have functioning kidney transplants. Amyloid deposits in DA contain fibrils, P-component (AP), and glycosaminoglycans (GAGS); fibrils are composed of polymerized beta-2 microglobulin (ß2m), which appears to be intact and not significantly proteolyzed. We present clinical, pathologic, and biochemical studies carried out on 7 patients with DA, all of whom had carpal tunnel syndrome, arthropathy and bone cysts, one of whom sustained a pathologic fracture related to DA and hyperparathyroid bone disease, and one of whom had macroglossia due to ß2m deposition systemically. Amyloid was isolated by water extraction from joint fluids (3), bone cysts (1), and synovial tissue (1) taken at the time of surgery, and ß2m identified on immunoblots of fibril preparations, saline supernatants, and residue dissociated on SDS-PAGE probed with epitope specific antibodies, anti-AP, and antibodies to modifications induced by Advanced Glycation End Products (AGE). Results were compared with (a) purified normal human ß2m, (b) soluble ß2m in joint fluid and dialysate of a patient with DA, (c) human ß2m produced by two full-length recombinant constructs (p714 and pHN1) expressed in high yield (~20 mg/l cells) in *E.coli*, and (d) AGE-modified (incubated with 0.1M glucose for 60 days) ß2m. Methodology was developed to separate monomeric from dimeric ß2m by differential salt elution; *in vitro* fibrillogenesis was monitored by congo red birefringence. These studies confirm the prevalence of aggregation and AGE-modification in DA; recombinant constructs will be used to analyze the importance of specific domains of the molecule critical to fibrillogenesis, whether AGE modification accelerates this process, and to develop *in vitro* and *in vivo* models of disease for further studies.

Cryoglobulinemic and Noncryoglobulinemic Neuropathy in Chronic Hepatitis C Virus (HCV) Infection. L. Wilson, B. Reichler, and P.D. Gorevic. Department of Medicine, Mount Sinai Medical Center, New York, NY.

Recent reports suggest that the overall clinical prevalence of peripheral neuropathy/myopathy may approximate 15% among patients chronically infected by Hepatitis C Virus (HCV), and may be the presenting feature of the disease. Neuropathy comprises one of an expanding spectrum of overlapping syndromes, including cutaneous vasculitis, joint disease, or nephritis, which are extrahepatic disease manifestations of HCV, not invariably associated with mixed cryoglobulinemia (MC) or advanced liver pathology. Although initial studies reported 7–15% patients with the syndrome of MC have neuropathy, more recent estimates based on electrophysiologic testing and/or biopsy have noted prevalences as high as 50–60%. 22 HCV RNA-positive patients (10 men and 12 women; mean age at diagnosis 34) seen over the period 1993–2000 were found to have neuropathy on the basis of detailed and serial testing. Other disease manifestations included purpura/livedoid vasculitis (68%), arthralgias/arthritis (64%), nephritis (23%), abnormal LFTs (68%), type II cryoglobulins (81%), positive RF (86%) and low C4 (62%). No correlation was found between neuropathy and specific disease manifestations, cryoglobulin quantitation, the presence of anti-phospholipid antibodies, HCV copy number, splenomegaly, retroperitoneal adenopathy, or the severity/stage of hepatitis on liver biopsy. All patients complained of lower extremity distal paresthesias/dysesthesias, with asymmetric upper extremity involvement noted in 11; other symptoms included burning, weakness and myalgias. Two patients presented with foot drop, and one with bilateral sensorineural hearing loss; 5 had elevated CPKs, and 0/9 tested were found to have antibodies to neuronal (ganglioside, MAG sulfatide, or Hu) antigens. Electrophysiologic studies (serial in several patients) disclosed a spectrum of multifocal lesions with small fiber predominance, asymmetric in all except two, entrapment neuropathy (3), or mononeuritis multiplex (3). We also found a significant incidence of autonomic involvement, manifest as orthostasis, sicca, erectile dysfunction, gastroparesis, and subjective temperature variability resembling raynauds. One patient with disabling peripheral and autonomic neuropathy consistently had no detectable cryoglobulins, and another only developed cryoglobulinemia on serial studies after neuropathy was well established. Long-term follow-up revealed that, once established, neuropathy may remain stable without therapy, and may respond gradually to HCV therapy or IVIG. HCV-associated neuropathy may be found to significantly exceed other extrahepatic manifestations when the full spectrum of subclinical disease is delineated.

Interleukin-1alpha (IL-1 α) Stimulates Differential Expression of Proteoglycans Secreted from Cellular Components of the Blood Brain Barrier (BBB). J.A. Ripellino and P.D. Gorevic. Division of Rheumatology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Alzheimer's disease is characterized pathologically by neurodegenerative changes, and distinct cerebrovascular abnormalities, such as thickening of the vascular basement membrane, loss of endothelial mitochondria, and activation of perivascular astrocytes and microglia. Activated glial cells overexpress proinflammatory cytokines (e.g., IL-1 and TNF), as well as oxidative stress-related enzymes such as inducible nitric oxide synthases (iNOS) that may play critical roles in AD-associated inflammation at sites of neuropathology, and in the progression of neurodegeneration. Primary abnormalities of cerebral microvasculature in AD have been suggested on the basis of ultrastructural (luminal narrowing, dilatation of vessels) and immunohistological studies. Heparan sulfates PGs (HSPGs) are important constituents of the vascular basement membrane, and as such contribute significantly to the integrity of the BBB. Although several different classes of PGs (i.e., heparan, dermatan, chondroitin and keratan sulfate) colocalize with amyloid in neuritic plaques, the major constituent of cerebrovascular amyloid appears to be HSPG. In this study, we present evidence that stimulation of components of the BBB, endothelial cells and glial cells, by IL-1 α results in altered metabolism of secreted and cell associated proteoglycans. Stimulation of glial cells by IL-1 α resulted in a dose dependent decrease of sulfate incorporation into both secreted and cell associated molecules. Proteoglycans purified from glial cells, which were in the presence or absence of IL-1 α by anion exchange chromatography eluted as two heterogeneous peaks at 0.66M and 1.02M NaCl. In the presence of IL-1 α the relative proportion of secreted proteoglycans present in the 0.66M pool decreased by 23% with a concomitant increase in the more negatively charged pool; whereas, cell associated proteoglycans demonstrated a 30% decrease in the more highly charged molecules with a proportionate increase in the less negatively charged proteoglycans. In contrast to primary glial cells, microvascular endothelial cell proteoglycans eluted as one peak at 1.25M NaCl. After IL-1 α stimulation, the secreted proteoglycans were eluted as single peaks, but at a higher NaCl concentration (1.6M NaCl). There was no change in the elution profile of the cell-associated proteoglycans. These results indicate that proinflammatory cytokine stimulation can change the molecular characteristics of proteoglycans derived from cells comprising the BBB. It is likely that changes in the composition of these extracellular matrices, basement membranes or cell surface molecules may contribute to the overall integrity of the BBB.

Ticlopidine-Induced SLE: A Report of Four Cases. R.F. Spiera, M.D.[1], R. Berman, M.P.H.[1], and H. Spiera, M.D[2]. [1]Department of Medicine, Beth Israel Medical Center, New York, NY; and [2]Department of Medicine, Mount Sinai Medical Center, New York, NY

Drug-induced lupus has been associated with a variety of medications. Ticlopidine is a platelet aggregation inhibitor which has been associated with thrombotic thrombocytopenic purpura. which is believed to be immune mediated. We now report 4 patients with systemic lupus erythematosus (SLE) occurring in the context of ticlopidine use, with a pattern of disease similar to that generally observed in drug-induced SLE. This is the first reported series of patients with ticlopidine-induced lupus, to our knowledge.

Four patients were evaluated between 1997 and 1999 with SLE, the onset of which followed institution of ticlopidine therapy. Mean age of onset of SLE in these patients was 70 years (range 63 – 74). Three of the patients were women. Clinical features included arthritis (4/4), pleuropericarditis (2/4), fever (1/4), and constitutional symptoms (4/4). None had renal disease, CNS disease, rash, or severe hematologic abnormalities. All 4 were ANA-positive, 3 of whom became ANA-negative with drug withdrawal. All had detectable anti-histone antibodies, which persist in two despite absence of clinical disease activity. Antibodies to double-stranded DNA were present in 3/4, all of whom became negative following drug withdrawal. All 4 were normo-complementeric throughout and following their disease course. All 4 required corticosteroid therapy, which was tapered with drug withdrawal. Only one patient remains on corticosteroid and methotrexate therapy, but at lower doses and with better disease control 10 months after discontinuing ticlopidine. Mean duration of clinical and serological improvement from time of drug withdrawal was 3 months (range 1.5 to 6 months).

The clinical features of these patients, namely older age of onset, prominence of pleuropericarditis and arthritis with paucity of CNS, renal, or skin involvement, and presence of detectable anti-histone antibodies is suggestive of drug-induced SLE. Moreover, all 4 patients had clinical and serological improvement following ticlopidine withdrawal, allowing cessation or reduction of corticosteroid therapy. We suspect that ticlopidine can cause drug-induced SLE, and that this exposure should be considered particularly in the evaluation of elderly patients with SLE.

Halofuginone Prevents the Development of Cutaneous Hyperplasia by Interfering with TGF-Mediated Signaling Events. T.L. McGaha[1], H. Spiera[2], and C.A. Bona[1]. Department of Microbiology[1], and Division of Rheumatology, Department of Medicine[2], Mount Sinai Medical Center, New York, NY.

Objective: The aim of the study was to examine the effect of halofuginone on the development of tight-skin (TSK) syndrome and investigate possible mechanisms of action. Methods: TSK/+ mice were injected with 1 g of halofuginone every other day for 60 days. The mice were then assessed for the development of TSK syndrome. The consequence of halofuginone treatment on collagen promoter activity and intracellular signaling was carried out in vitro on primary fibroblasts cell culture. The effects of halofuginone on collagen promoter activity were determined by Northern blot and by using a reporter plasmid containing the collagen (2) typeI promoter. The effect of halofuginone on TGF- signaling was determined by Western, electrophoretic mobility shift assay (EMSA), and by a reporter assay utilizing the TGF- responsive reporter construct 3-TPLux.

Results: Halofuginone prevented the development of cutaneous hyperplasia in both adult and neonatal TSK/+ mice. However, only newborn animals treated with halofuginone exhibited a significant decrease in dermal hydroxyproline content. Interestingly, C57BL/6 mice treated with halofuginone exhibited skin thickness and dermal hydroxyproline content similar to untreated mice. In addition, reporter gene assay demonstrated that halofuginone elicits its effect, at least in part, by reducing activity of the collagen (2) typeI promoter. Western blot, EMSA, and reporter gene analysis showed that halofuginone treatment drastically reduces the ability of TGF-1 to stimulate fibroblasts.

Conclusions: Halofuginone inhibits the excessive production of extracellular matrix and prevents skin sclerosis when administered to TSK/+ mice after birth as well as decreasing sclerosis in adult animals. In addition, halofuginone treatment had no effect on normal matrix productions, suggesting that it may be a potentially powerful therapeutic tool in treatment of fibrotic disease. The molecular analysis of pathways important in typeI collagen production demonstrated that halofuginone interferes with the activity of the typeI collagen promoter and this effect is likely due to the ability of halofuginone to interfere with TGF-induced stimulation of collagen production.

Spinal Cord Research

Maximal Arm Ergometry Exercise Testing in Monozygotic Twins Discordant for Paraplegia. Ann M. Spungen, Ed.D.[1,2], Grimm D.R., Ed.D.[1,2], Drexler H., B.S.[1,2], and Bauman W.A., M.D.[1,2]. Mount Sinai School of Medicine, New York, NY, and Veterans Affairs Medical Center, Spinal Cord Damage Research Center, Bronx, NY.

Persons with spinal cord injury (SCI) are dependent on their arms for daily activity and exercise. Unlike leg work, normative data for arm ergometry is limited. In order to control for genetic differences, our goal was to determine the response to maximal arm ergometry exercise testing in twins with paraplegia compared with their monozygotic co-twins who were not paralyzed. Genetic testing for zygosity was performed (Lifecodes Corp., Stamford, CT). Arm ergometry testing consisted of a 12 watt/minute (60 rpm) incremental exercise protocol to maximal exertion, as defined by achievement of about 85% of maximal predicted heart rate (HR) and a respiratory exchange ratio (RER) of 1.1. Exercise testing was performed on a Fleisch Universal ergometer (Epalinges, Sweden). Gas exchange analysis was determined by a metabolic cart (System 2900, SensorMedics Inc., Yorba Linda, CA). Venous plasma lactate production was measured during each minute of exercise (2200 Stat, YSI Inc., Yellow Springs, OH). Ten pairs of monozygotic twins were studied (4 female and 6 male). All twins with paralysis had lower paraplegia (T7-L2) and were injured for 13±10 y. The mean±SD age of the total group was 36±8 y. The SCI twins weighed significantly less than their able-bodied co-twins (64.1±13.1 vs. 71.6±17.2 kg, $p<0.01$). Pre-exercise HR was significantly higher in the SCI twins than their able-bodied co-twins (90±18 vs. 81±11, $p<0.05$), all other metabolic and hemodynamic parameters were not different between the twins. At the same workloads (minutes 1 – 8), submaximal HRs were significantly higher for the SCI twins compared with their co-twins. HR at the anaerobic threshold was significantly higher in the SCI twins (149±17 vs. 121±6,

$p<0.0005$). At peak exercise, workload, metabolic and hemodynamic values including HR, were not different between the twins.

In conclusion, higher pre-exercise HRs may indicate reduced fitness levels in those with SCI. In addition, the increased sub-maximal HRs in the SCI twins may be related to decreased venous return represented by attenuated stroke volume, reduced elastic vessel wall compliance, and loss of the muscle pump, i.e., blood "pooling" in the lower extremities during exercise.

Venous Vascular Function of the Forearm Is Preserved in Paraplegia. Jill M. Wecht, Ed.D.[1,2], DeMeersman R.E., Ph.D.[3], Weir J.P., Ph.D.[4], Bauman W.A., M.D.[1,2], and Grimm D.R., Ed.D.[1,2]. Mount Sinai School of Medicine, New York, NY; Veterans Affairs Medical Center, Spinal Cord Damage Research Center, Bronx, NY; Columbia University, New York, NY; and Des Moines University, Osteopathic Medical Center, Des Moines, IA.

We previously reported significantly altered venous vascular function in the lower limbs of subjects with paraplegia compared with able-bodied controls. These alterations have been attributed to the combination of autonomic disruption, immobility and inactivity. This study compared the venous vascular function of the upper limbs (forearms) between subjects with paraplegia and able-bodied controls before and after an isometric handgrip test. An additional objective was to quantify the difference in vascular function between the denervated and innervated limbs in subjects with paraplegia.

Twelve healthy males with low level paraplegia (T6–T12) were compared with eight able-bodied males of similar age, height and weight. Venous occlusion plethysmography was used to evaluate venous capacitance, emptying rate, total outflow and compliance before and after isometric contraction using a handgrip dynamometer equaling 30% of each subject's maximal voluntary handgrip contraction (kgm).

Controlling for height, weight or body mass index, arm circumference was significantly greater in subjects with paraplegia than in able-bodied controls (31.7±6.8 vs 28.2±2.8 cm; $p<0.01$). No differences were evident in vascular function prior to or following isometric contraction. Significant differences were demonstrated between all pre- and post-contraction vascular parameters for both groups, and the % changes from pre- to post-contraction were similar between groups. Resting vascular function, including capacitance, total outflow and compliance, were significantly different between the arms and legs in subjects with paraplegia. In contrast, only total outflow was significantly different between the calf and forearm in able-bodied controls.

This study demonstrated that venous vascular function in the forearm is preserved in individuals with paraplegia, both at rest and following provocation. As expected, vascular function in the denervated limbs was a fraction of that in the innervated limbs, which further supports the deleterious effect of spinal cord injury on denervated vessels. Larger arm circumferences in the paraplegia group, when controlling for other indices of body size, suggests that pushing a wheelchair for daily mobility enlarges forearm skeletal muscle without significantly affecting peripheral vascular function.

With ALS Airway Hyperreactivity Is Related to Airway Caliber. Erwin J. Oei, M.D.[1,3], Grimm D.R., Ed.D[1,2], Chandy D., M.D.[1], Schilero G.J., M.D.[1,4], and Lesser M.L., M.D.[1,3]. Mount Sinai School of Medicine, Department of Medicine, New York, NY; Veterans Affairs Medical Center, Spinal Cord Damage Research Center, Bronx, NY; Veterans Affairs Medical Center, Pulmonary Department, Bronx, NY; and Veterans Affairs Medical Center, Critical and Operative Care, Bronx, NY.

Introduction: The pathogenesis of airway hyperreactivity (AHR) among subjects with tetraplegia remains unclear. Possible causative factors include unopposed bronchoconstrictive parasympathetic (cholinergic) activity due to loss of modulating sympathetic innervation which arises at the level of T1 –T6, and/or inability to stretch airway smooth muscle with deep inspirations because of reduced inspiratory capacity associated with respiratory muscle paralysis. To differentiate between these two etiological possibilities, subjects with amyotrophic lateral sclerosis (ALS) were selected for this study because they develop progressive restrictive ventilatory impairments as the disease progresses, whereas autonomic nervous system function remains intact.

Methods: We studied 23 non-smoking ALS patients with no history of allergies, atopic disorder, asthma or recent pulmonary infections. The patients were subjected to methacholine bronchoprovocation by a standardized method currently used for assessment of AHR among subjects with tetraplegia. A PC_{20} value of <8 mg/ml was considered indicative of AHR.

Results: We found that 0 of 7 subjects with a forced vital capacity (FVC) greater than 80% predicted (%) demonstrated AHR. In contrast, 8 of 16 subjects with a FVC less than 80% exhibited AHR. Regression analysis of data obtained from the 16 subjects revealed no relationship between PC_{20} and FVC (%), $r=0.112$, $p=0.679$. However, there were significant relationships between PC_{20} and FEV_1(%), $r=0.500$, $p=0.048$, FEF_{25-75} (%), $r=0.771$, $p=0.005$; and FEF_{25-75}(%)/FVC(%), $r=0.55$, $p=0.027$. FEF_{25-75}(%)/FVC(%) is considered a surrogate measure of airway size in relation to lung size.

Conclusions: Although 50% of subjects with reduced FVC had AHR, the underlying process contributing to AHR was not decreased lung volume but reduced baseline airway caliber and/or reduced airway size relative to lung size. Similarly, it has been observed among subjects with tetraplegia that AHR correlates with reduced FEF_{25-75}(%), FEV_1(%) and FEF_{25-75}(%)/FVC(%). The findings from the current study suggest that reduced airway caliber among subjects with tetraplegia may not be due solely to reduced lung volumes or unopposed cholinergic activity.

Vasculotoxic Plasma Homocysteine Levels in Persons with SCI. William A. Bauman, M.D.[1,2], Adkins R.H., Ph.D[3], Kemp B.J., Ph.D.[3], and Herbert V., M.D.[2]. Mount Sinai School of Medicine, Department of Medicine, New York, NY; Veterans Affairs Medical Center, Spinal Cord Damage Research Center, Bronx, NY, and Ranchos Los Amigos National Rehabilitation Center, Downey, CA.

Coronary vascular disease (CVD) is a leading cause of morbidity and mortality in persons with chronic SCI. Previous studies from our group have defined a dysmetabolic syndrome in those with SCI. Elevated plasma homocysteine levels have been recognized for a decade as an independent risk factor for vascular disease (Clarke et al. NEJM, 324:1149–55, 1991). Hyperhomocysteinemia may occur as a result of enzyme defects. However, the most common causes of hyperhomocysteinemia are due to inadequate ingestion or absorption of folate and/or vitamin B_{12}, producing impairment of remethylation of homocysteine to methionine.

Concentrations were determined as part of their annual physical examination. Plasma homocysteine concentrations were studied in 845 subjects with SCI divided by gender, ethnicity and level or completeness of injury. There were 723 (85.5%) men and 122 (14.5%) women. Ethnic distribution was 193 (22.9%) white, 203 (24.1%) African-American, 417 (49.4) Latino, and 30 (3.6%) other. Values were stratified as less than 15.17 nmol/ml and greater than 20 nmol/ml. A homocysteine value greater than or equal to 15.17 nmol/ml was designated as being elevated. In the men, 221 (30.5%) had values that were elevated and 79 (10.9%) had values greater than 20 nmol/ml. In the women, 13 (10.6%) had values that were elevated and 2 (1.6%) had values greater than 20 nmol/ml. The three major ethnic groups for men with elevated values are as follows: whites had 63 (38%), African-Americans had 57 (34.4%), and

Latinos had 93 (25.3%) ($X^2=9.64$, $p<0.008$). Plasma homocysteine was found to correlate with advancing age in men ($p<0.018$) and women ($p<0.004$). There was no significant difference in distribution by neurological deficit. Because these individuals may have multiple other independent risk factors for CVD, patients found to have elevated concentrations of plasma homocysteine should receive a trial course of oral folic acid, 400 μg daily, and vitamin B_{12}, 100 μg daily, and if ineffective, B_6, in an attempt to reverse this elevation.

Coronary Artery Calcification in Persons with Spinal Cord Injury. Matthew J Budoff, M.D.[1], Aref S., M.D.[1], Adkins R.H., Ph.D.[2], Yee F., Pharm.D.[2], Bakhsheshi H., R.T.[1], and Bauman W.A., M.D.[3,4]. Harbor-UCLA, Los Angeles, CA; Ranchos Los Amigos National Research Center, Downey, CA; Mount Sinai School of Medicine, New York, NY; and Veterans Affairs Medical Center, Spinal Cord Damage Research Center, Bronx, NY.

Persons with spinal cord injury (SCI) have been reported to have an increased prevalence of premature cardiovascular disease. We used electron beam tomography measures of coronary calcium to estimate the prevalence and amount of coronary atherosclerosis. We studied defferences in 27 persons with SCI, as compared to a matched cohort of asymptomatic persons. The 81 controls were 3:1 matched for age, gender, ethnicity and cardiac risk factors. Patients were enrolled who had SCI of over one year duration, and underwent electron beam tomography of the coronary arteries, as well as studies of lipid levels and homocysteine.

Those with SCI varied in age from 29–59 (mean 47.7±8 years). We studied 24 men, 3 women with chronic SCI including 63% Hispanic and 11% African American. The mean calcium score of the SCI group was 17±20 (range 0–87), significantly greater than the control group (8±11, $p<0.05$). The prevalence of coronary calcium was greater in the spinal cord damage population than the control population, although not statistically significant (33% vs. 22%, $p=0.24$).

There was one coronary event in the SCI group (coronary death) with a patient with a score of 51 (signifcantly greater than average for age and gender). This study demonstrated that persons with chronic spinal cord injury have premature and advanced atherosclerosis as compared to similar persons without spinal cord injury. A larger study is underway to assess the prevalence and severity of atherosclerosis.

Queens Hospital Center

Bilateral Internuclear Ophthalmoplegia in the Primary Antiphospholipid Antibody Syndrome. J. Ameh, M. Choksi, A. Munir, I. Ashley, and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Antiphospholipid syndrome (APLS) is being diagnosed with increasing frequency, in spite of its protean manifestations (that is, mimics a variety of clinical disorders), because of increasing awareness among clinicians of this syndrome. We report a unique case of primary APLS with recurrent thrombosis and a brainstem infarct causing bilateral internuclear ophthalmoplegia (BINO). APLS was confirmed serologically.

Case Report: A 52-year-old Haitian woman was hospitalized on June 16, 1999 because of gait instability of one day's duration. There were no other associated symptoms. Past medical history was significant for a spontaneous abortion in 1980, a cerebrovascular accident with central loss of vision in 1997, and a right lacunar infarct in the internal capsule with residual left upper extremity paresis in 1998. The patient had been taking 81 mg aspirin daily since 1997. Physical findings included gait instability, left upper extremity mild monoparesis, left pronator drift, left facial paresis and mild dysarthria. Computerized tomographic (CT) scan of the brain showed a lacunar infarct in the anterior limb of the right internal capsule. A hypercoagulable state was suspected and pertinent laboratory data confirmed the diagnosis of APLS. Anticardiolipin antibody level was 42.6 (<23 mcg/mL). Antithrombin III, serum protein C and protein S activity levels were normal. The patient was anticoagulated with unfractionated heparin. Magnetic resonance imaging showed an area of hypoattenuation in the pons and medulla suggestive of an infarct. The next day, the patient developed BINO with worsening dysarthria and left facial palsy, followed within 24 hours by dysphagia and left hypoglossal palsy. A feeding tube was inserted to prevent aspiration. On the fourth day of hospitalization, the patient developed acute respiratory distress and hypoxic respiratory failure. A normal ventilation perfusion scan essentially ruled out a pulmonary embolus and a repeat CT scan of the brain did not show intracranial bleeding. The patient was treated for aspiration pneumonitis and later for a massive upper gastrointestinal hemorrhage. All efforts to wean her off the respirator were unsuccessful. The patient was transferred to a nursing home.

Discussion: Considerable clinical and research interest continues to be generated by APLS and other causes of thrombosis. Rapid clinical progression despite adequate anticoagulation indicates the need for further study regarding optimal approaches to therapy. Accurately identifying subsets of patients with APLS who are at highest risk of developing a major thrombosis is important in order to institute appropriate preventive measures.

Sarcoidosis with Multiple Large Hepatic Cystic Lesions. R.M. Ayinla, R. Ahmed, H. Rahman, J. Fleischman, and F. Rosner. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Sarcoidosis is a multisystem disorder of unknown etiology, most commonly affecting young adults. The clinical spectrum of sarcoidosis is protean, but pulmonary manifestations typically dominate. Hepatic granulomas may also occur. The incidence of hepatic involvement is reported to be 50–90%. We describe a patient with sarcoidosis and multiple hepatic cystic lesions.

Case Report: A 38-year-old man presented with a two-week history of bilateral lower extremity swelling, generalized weakness, and arthralgias involving multiple large joints. These symptoms had occurred intermittently over a period of 5 years. Physical examination was remarkable only for hepatomegaly and bilateral pitting edema of the legs. Liver function tests showed elevated alkaline phosphatase and gamma-glutaryl transpeptidase (400 IU/L and 233 U/L, respectively). Abdominal computed tomographic scan revealed massive hepatomegaly (25 cm) with multiple large cystic lesions and necrosis, internal septations and sharply outlined borders. On open liver biopsy, multiple coalescing epithelioid granulomas were seen with central necrosis involving lobules, portal tracts and periportal areas. Acid-fast bacillary and fungal stains were negative. Serum angiotensin-converting enzyme (ACE) level was elevated. Whole body gallium and Kveim tests were positive. The patient's symptoms and the hepatic lesions resolved spontaneously without any specific treatment.

Conclusion: Sarcoidosis can present with multiple large cystic lesions in the liver. Initial work up of such lesions should focus on infectious and malignant etiologies. However, sarcoidosis should be included in the differential diagnosis of cystic liver lesions. If the diagnostic testing is inconclusive, serum ACE level, gallium scan and Kveim test may be helpful.

Dicloxacillin-Induced Acute Interstitial Nephritis. A. Bawa, H. Dhingra, and F. Rosner. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Acute Interstitial Nephritis (AIN) is an inflammatory renal disease predominantly affecting the tubules and the interstitium. AIN is most often caused by drug therapy, although legionella, leptospirosis, streptococcal and viral infections, and sarcoidosis may also be responsible. A variety of drugs have been implicated, including numerous chemotherapeutic agents and nonsteroidal, anti-inflammatory drugs. We describe a case of dicloxacillin-induced AIN.

Case Report: A 34-year-old HIV-positive man was hospitalized because of a pruritic rash of one day's duration on both legs. The patient had not been taking any medications for his HIV status. He denied smoking, alcohol intake or use of any recreational drugs. The patient had been taking dicloxacillin for two weeks, prescribed for a superficial ulcer on his penis. His blood pressure was 120/70 mmHg, pulse rate 84/min regular, respiratory rate 16/min and temperature 100.8°F. There was an erythematous nonpruritic purpuric rash on both legs extending up to the thighs. The white blood cell count was 4,300 per mm^3, hemoglobin 11.2 g/dL, hematocrit 32.1%, platelets 100,000/mm^3, and a differential of 34 neutrophils, 33 lymphocytes, 11 monocytes and 22 eosinophils. Routine blood chemistry tests were normal except for blood urea nitrogen of 20 mg/dL and serum creatinine of 1.4 mg/dL. There were 100 red blood cells per high power field on urine analysis, without any casts or protein. Tubulo interstitial nephritis was diagnosed. Skin biopsy of the pruritic rash showed leukocytoclastic vasculitis consistent with a hypersensitivity reaction. The urine eosinophil test was positive. Dicloxacillin was discontinued. The patient's rash improved and the fever subsided.

Discussion: The diagnostic triad of fever, skin rash and peripheral eosinophilia is highly suggestive of AIN. In view of the clinical scenario and laboratory evidence, the diagnosis of AIN was made and renal biopsy was deferred. The beta lactam group of antibiotics is the most studied group of antibiotics associated with AIN. However, only a few cases of dicloxacillin-induced AIN have previously been reported. Discontinuation of the offending drug is usually curative, with reversal of all signs and symptoms of AIN, as occurred in our patient.

Stress among Internal Medicine Residents. A. Briones, F. Rosner, and D. Brennessel. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Background: Residency training generates physical, emotional and mental tensions that may affect the residents' performance. While stress may compromise optimum performance, it may simultaneously stimulate the acquisition of knowledge, good attitudes and skills.

Objectives: (1) To measure and compare the levels and types of stress among all three postgraduate-year (PGY) level internal medicine residents. (2) To identify the least and most stressful factors in our residency programs.

Methods: All 70 internal medicine residents, 45 from Queens Hospital Center (QHC) and 25 from Elmhurst Hospital Center (EHC), with a mean age of 32 years (range 25–40), participated in this study. They answered a 40-item questionnaire which enumerates potential stress factors in a residency program. The factors were grouped into the following categories: (1) situational/environmental stress, (2) professional stress, and (3) personal stress. Each factor was rated on a scale of 0 to 5 (0 the least stressful and 5 the most stressful). Six months later, the same questionnaire was administered again only to the QHC residents. The paired, two-tailed t-test was used to compare the residents' responses (first responses versus second responses). One-way Analysis of Variance with Turkey's Multiple Comparison Test was used to compare the responses of each PGY level.

Results: There was no significant difference between the PGY-1s' first and second responses. However, there was a significant difference between the PGY-2s' and PGY-3s' first and second responses, $p<0.05$. Lack of time for in-depth learning, excessive paperwork, lack of time with family and friends, lack of time for personal interests/pursuits and poor support services were the five most stressful factors. Marital problems, disagreements with attending physicians, lack of respect from other residents, lack of faculty support, and psychosocial problems were the five least stressful factors. Situational stresses ranked the highest, followed by professional stresses and then by personal stresses. Mean scores for all PGY levels were as follows: PGY-1: 1.99; PGY-2: 2.35 and PGY-3: 2.47.

Conclusion: Internal medicine residents have different levels and natures of stress during each of the three years of training. Among medical residents from two inner city public hospitals, the level of stress is lowest among PGY-1 residents and highest among PGY-3 residents. The increasing level of stress can be attributed to the growing levels of responsibility a resident shoulders while progressing from internship to senior year. Stress levels in the beginning of the academic year decreased toward the latter part of the year among the PGY-2 and PGY-3 residents. Stress among PGY-1 residents did not change significantly, probably because of the continuous pressure and anxiety that is inherent in internship. Situational and professional factors were considered highly stressful, while personal factors were rated less stressful.

Acute Lupus Pneumonitis and Lung Bulla as the First Manifestations of Systemic Lupus Erythematosus (SLE). M. Choksi, N.A. Adhami, and R.M. Ayinla. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Acute lupus pneumonitis with typical radiographic findings of patchy infiltrates is an uncommon manifestation of systemic lupus erythematosus (SLE). We report a previously healthy 18-year-old Indian woman who presented with pancytopenia, malar rash and radiographic findings of a giant right-sided bulla with bilateral patchy infiltrates.

Case Report: An 18-year-old Indian woman presented with a 10-day history of fever, dry cough, weakness and dyspnea on exertion. She denied smoking and alcohol use, and had never been sexually active. Her temperature was 102°F and her respiratory rate 22/min. She had decreased breath sounds and resonant percussion in the right hemithorax. The leukocyte count was 1900 cells/μL, hemoglobin 8.7 g/dL and platelets 40,000/μL. Routine blood chemistry panel, liver function tests (LFTs), hepatitis profiles for A, B and C, and blood cultures were negative. There was normal cellularity on bone marrow biopsy. Arterial blood gas (ABG) testing found a pH of 7.41, Pa_{CO2} of 29 torr and Pa_{O2} of 98 mmHg. Pulmonary function testing (PFT) demonstrated a markedly reduced diffusing lung capacity for carbon monoxide (DL_{CO}) (42%). A giant right-sided bulla with patchy infiltrates at the right base and in the left lung was seen on a chest radiograph. A chest computerized tomographic (CT) scan also showed a single large bulla with bilateral patchy infiltrates and no lymphadenopathy. Purified protein derivative test was negative but the anergy panel was positive. The patient was empirically treated with doxycycline and ciprofloxacin, with resulting defervescence of fever and clinical improvement. She was discharged home but readmitted 3 weeks later with high-grade fever (104°F), maculopapular facial rash, worsening shortness of breath and cough. She denied joint pain, swelling or pleuritic chest pain. A complete blood cell count revealed persistent pancytopenia. ABG showed hypoxemia (Pa_{O2} 60 mmHg) with an elevated A-a gradient of 50. LFTs revealed increased aspartate aminotransferase of 360 U/L, increased alanine aminotransferase 216 U/L, gamma-glutamyl transpeptidase 94 U/L and alkaline phosphatase 52 U/L. A bronchoscopy with bronchoalveolar lavage was performed, which was negative for bacteria, acid-fast bacilli, *Pneumocystis carinii* and fungi. The patient was treated with ceftazidime, without clinical improvement. A connective tissue disease work up revealed antinuclear antibody 2+ (homogenous), anti-DNA antibody positive (titer 1:80), Smith antibody positive, anti-smooth-muscle antibody positive (titer 1:40), and low complement: C3-17 mg/dL (normal 104–187 mg/dL) and C4< 10 mg/dL (normal 104–187 mg/dL). The diagnosis of lupus pneumonitis was made, and hydrocortisone was started with rapid clinical and radiographic improvement. The patient was discharged home on prednisone and hydroxychloroquine. Repeat PFT revealed normalization of her DL_{CO} (80%).

Discussion: SLE is a multi-system disease of unknown etiology characterized by the presence of numerous autoantibodies. Respiratory involvement ranges from asymptomatic pleuritis to life-threatening pneumonitis or pulmonary hemorrhage. Acute lupus pneumonitis typically occurs in patients with established

SLE, although it may occasionally be the initial manifestation of the disease. Patients typically present with fever, cough and shortness of breath, with radiographic findings of bilateral patchy infiltrates. Because respiratory infection is the most common cause of pulmonary infiltrates, infectious etiologies should be ruled out. Findings on high-resolution CT scan include thickened interlobular septa, parenchymal bands, bronchiectasis or subpleural bands. Emphysema with bullous lung changes have also been reported, as was the case in our patient.

Colonic Lipoma Presenting with Massive Hemorrhage. C. Li, K. Miller, E. Popa, M. Sharma, L. Kasturi, and S. Chokhavatia. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Lipomas are mature adipose tissue tumors, which may occur throughout the gastrointestinal tract, usually submucosally. Colonic lipomas are common but only rarely symptomatic, manifesting with abdominal pain or chronic blood loss.

Case Report: A 47-year-old Guyanese woman presented with a two-month history of right upper quadrant pain, maroon stools, increasing fatigue, weakness and a 10-pound weight loss. On examination, she had conjunctival pallor, a 5-cm firm, nontender right upper quadrant mass and bright red blood on rectal examination. The hemoglobin was 5.4 g/dL (12 – 16g/dL) and mean corpuscular volume (MCV) 86 fL (81 – 99 fL). The patient was treated with intravenous fluid and packed erythrocyte transfusions. Colonoscopy showed a large ulcerated mass at the hepatic flexure which could not be transversed, raising the possibility of colonic carcinoma. Computed tomographic scan confirmed a 5.2 x 2.7 cm mass. The patient underwent a right hemicolectomy. Macroscopically the specimen was a centrally ulcerated submucosal mass, histologically consisting of mature adipose tissue. There was no evidence of carcinoma.

Conclusion: Lipomas rarely present with massive bleeding. Even ulcerated lesions usually produce only occult bleeding. Surgical intervention is recommended for symptomatic lipomas with massive bleeding, for intussusception and bowel obstruction, and for very large polyps when there is suspicion of colonic carcinoma.

Microscopic Polyangiitis Presenting as Idiopathic Pulmonary Fibrosis: Case Report. I. Mansi, A. Opran, D. Sondhi, R. Ayinla, and F. Rosner. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Antineutrophil cytoplasmic antibody (ANCA)-related small vessel vasculitis is increasingly diagnosed as a cause of pulmonary renal syndrome. We report a patient with microscopic polyangiitis who presented with idiopathic pulmonary fibrosis, and developed hematuria and proteinuria approximately one year later.

Case Report: A 55-year-old woman presented with fever, cough, and yellowish sputum. She had crackles bilaterally at the lung bases. High resolution computed tomography scan of the chest was consistent with idiopathic pulmonary fibrosis. A year later, urinalysis showed proteinuria and microscopic hematuria. The serum level of perinuclear ANCA was high. Renal angiogram was normal. Renal biopsy showed pauci-immune crescentic glomerulonephritis. The diagnosis of microscopic polyangiitis was made. After the patient received immunosuppressive therapy, there was marked improvement.

Conclusion: Work up for diagnosis of small vessel vasculitis is important in the differential diagnosis of idiopathic pulmonary fibrosis.

Interferon Treatment Outcome of Hepatitis C in a New York City Municipal Hospital over a Ten-Year Period. N. Murillo, L. Kasturi, S. Chokhavatia, and F. Rosner. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: More than four million Americans are currently infected with hepatitis C virus. In approximately 85% of patients, acute hepatitis C virus infection progresses to a chronic stage, which in time may lead to cirrhosis and liver cancer. Hepatitis C is responsible for 8,000 – 10,000 deaths annually and is the leading reason why people receive liver transplants. Current therapy for hepatitis C, although effective in some patients, is problematic and still evolving. Monotherapy with interferon A (IFN-α2b) leads to a sustained serum alanine aminotransferase (ALT) response rate in 9 – 16% of patients and a sustained hepatitis C virus RNA response rate in 7 – 8% of patients.

Purpose: To identify patient characteristics and treatment results when interferon A is used, at a New York City municipal hospital.

Methods: We performed a retrospective chart review of patients diagnosed with hepatitis C virus antibody by ELISA. These patients were identified by a computer-generated database of discharge diagnoses from 1990 – 1999. Only charts with documented referral and follow up in the GI clinic were included in the study.

Results: Two hundred one patients had tested positive for the hepatitis C virus antibody by the ELISA test. Fifty-six of these patients were referred to the GI service for further evaluation. Of this group, 22 patients were eligible for treatment with interferon A (11 women and 10 men). There were 10 African Americans, 5 West Indians, 4 Hispanics, 2 Asians and one Caucasian. The age range was 40 – 70 years. The modes of acquisition of the virus included intravenous drug abuse (8), blood transfusion (3), sexual contact (2) and unknown (9). Serum ALT levels ranged from 56 to 258 units at the beginning of treatment. Twelve patients had stage 1, eight patients had stage 2, one had stage 3 and one had stage 4 chronic hepatitis C. All patients received interferon A, 3 million units subcutaneously, 3 times a week for from 3 months to 18 months, with an average duration of 12 months. Three patients had a sustained biochemical response (normalization of ALT) to treatment. None of them had sustained virological response.

Conclusion: Primary care physicians identified 56 of 201 (27%) patients testing positive for hepatitis C antibody as potential candidates for treatment. GI consultants found that less than half of these 56 patients were eligible for interferon A treatment. Less than 14% of these candidates (3 of 22) had a sustained ALT response to treatment. The patients' hepatitis C genotypes were not determined, since this study was an experimental tool at the time. None of the patients had a virological response. These findings are consistent with the previously reported poor rate of response of hepatitis C virus to interferon as monotherapy.

Correlation between the American Board of Internal Medicine In-Training Examination and Monthly In-House Examinations in Predicting Resident Score Performance. G. Peress. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Purposes: To review the results obtained on a series of monthly in-house examinations (IHEs) given at all levels of postgraduate training by the Queens Hospital Center of the Mount Sinai School of Medicine internal medicine training program, and to compare them to the results the residents achieve on the American Board of Internal Medicine In-training Examination (ITE).

Methods: Each year, medical residents at all levels of postgraduate training are given monthly IHEs in each of the different medical subspecialties. Each examination consists of multiple-choice questions that test skills in data recall, data interpretation, diagnosis and/or treatment, and clinical decision making, as it pertains to the particular subspecialty being tested for that month.

Results of ITEs and IHEs for the academic years 1997 – 1998 and 1998 – 1999 were reviewed, and residents' scores in each postgraduate year (PGY) class were compared amongst themselves. A numerical rank was assigned to each resident (i.e., the highest scorer received a rank of one; the second highest scorer a rank of two, etc.). Each resident was assigned two ranks, one based on the score achieved on the ITE and the other based on the yearly average score for the monthly IHEs. A total of six ranking groups were thus obtained for each academic year, corresponding to the IHE and ITE scores for PGY-1, PGY-2, and PGY-3.

In each academic year, the rank on the IHE for each resident was compared to his/her ITE rank, according to PGY class.

Results: Using the Spearman Rank Test, a high concordance (ρ) was found between the numerical rank the residents achieved on the IHE compared to that of the ITE. In both academic years, this concordance was highest in the PGY-3 classes, with $\rho=0.92$ in 1997–1998 and $\rho=0.70$ in 1998–1999, and was statistically significant ($p>0.0001$ and $p>0.002$, respectively). Concordance for the PGY-1 and PGY-2 classes in 1997–1998 were $\rho=0.52$ and $\rho=0.84$ ($p>0.054$ and $p>0.0001$, respectively), and in 1998–1999 were $\rho=0.67$ and $\rho=0.64$ ($p>0.013$ and $p>0.027$, respectively).

Conclusion: The IHE is a fairly reliable tool with which to predict which residents will score highest and which will score lowest on the ITE, especially in the PGY-3 classes.

Echinococcus Liver Cyst Successfully Treated with Oral Albendazole.

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Introduction: Echinococcosis of the liver is an uncommon disorder in the United States and rare in individuals who have resided in this country for more than a decade. The diagnosis is based on ultrasound or computed tomography (CT) findings of cystic lesions containing daughter cysts (water lily sign).

Case Report: We successfully treated a 49-year-old Nicaraguan woman who had resided in the United States for twelve years for an echinococcal liver cyst. The patient was evaluated for right upper quadrant discomfort. The patient had no history of recent travel outside the United States. Her only medications were conjugated estrogens/medroxyprogesterone for treatment of menopausal symptoms. Physical examination was unremarkable. Ultrasound examination of the abdomen revealed a cystic mass in the right lobe of the liver. CT of the abdomen showed a hypodense oval mass in the right hepatic lobe with peripheral enhancement. On magnetic resonance imaging, a cyst containing debris was noted. The patient's serology was positive for echinococcus antibody and negative for *Entamoeba histolytica*. A presumptive diagnosis of echinococcal liver cyst was made and the patient was treated with two cycles of oral albendazole 400 mg twice daily for six weeks. The cyst resolved and completely disappeared on the sonogram done six months later.

Conclusion: Medical treatment with oral albendazole alone, without the need for aspiration or surgical resection, may be successful in the early stages of echinococcus liver cysts.

Long-Term Efficacy and Safety of Cerivastatin (Baycol) in Type 2 Diabetes Mellitus.

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Background: Cerivastatin is a hepatic hydroxymethyl glutaryl coenzyme A (HMG COA) reductase inhibitor which decreases cholesterol synthesis. Cerivastatin is safe, effective and well tolerated in the long-term treatment of secondary hypercholesterolemia.

Objective: To examine the efficacy and safety of daily oral cerivastatin 0.3 mg on lowering serum cholesterol and LDL levels and on increasing HDL levels in type 2 diabetes mellitus (DM) patients.

Methods: Twenty patients with type 2 DM were enrolled in the study (12 women and 8 men). Lipid profile, liver function tests, creatine phosphokinase (CPK), and glycosylated hemoglobin (HbA_{1c}) levels were determined before initiation of treatment and one year later.

Results: Three patients were removed from the study because of abnormal liver function tests (2 patients) and elevated CPK level (1 patient). Of the 17 patients who completed the study, baseline total cholesterol ranged between 181 and 267 mg/dL (mean 239.70 ± 8.4 SEM), LDL 124–253 mg/dL (mean 158.17 ± 6.8 SEM), HDL 28–70 mg/dL (mean 47.69 mg/dL ± 2.8 SEM), and triglycerides (TG) 72–579 mg/dL (mean 214.8 ± 31.4 SEM). After one year of therapy, the total cholesterol decreased to a range of 95–251 mg/dL (mean 202.7 ± 9.4 SEM), with a mean reduction of 37 (15.4%, $p=0.003$), LDL 60–186 mg/dL (mean 120.23 ± 7.5 SEM), with a mean reduction of 38.94 (24.4%, $p=0.001$), HDL 31–86 mg/dL (mean 51.47 ± 4.2 SEM), with a mean increase of 3.82 (7.9%, $p=0.1$), and TG 69–281 mg/dL (mean 165.41 ± 18.5 SEM), with a mean reduction of 49.41 (22.9%, $p=0.08$).

Conclusion: Our study demonstrates that long-term cerivastatin therapy is effective and safe in reducing total cholesterol, LDL and triglycerides, and in increasing HDL in patients with type 2 diabetes mellitus and secondary hypercholesterolemia. The drug may cause liver and muscle toxicity.

Self-Reported Adherence to HIV Antiretroviral Therapy: Intervention to Improve Adherence Using a Clinical Pharmacist Model in an Outpatient Setting.

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Background: Adherence to HIV antiretroviral therapy is essential for successful suppression of detectable viral replication and preservation of the immune system. Suboptimal adherence (<95% of medication doses) increases the likelihood of virologic failure and the development of resistant viral strains.

Objectives: A performance-improvement project was developed to assess the need for intervention in order to increase patient adherence to HIV antiretroviral therapy (ARVT). The effectiveness of a clinical pharmacist model, in an outpatient setting, to improve medication adherence was evaluated.

Methods: Patients newly initiating ARVT (naive) and already receiving ARVT (experienced) were interviewed at baseline and follow-up visits by a dedicated clinical pharmacist in the immunology clinic at Queens Hospital Center (QHC) between January and April 2000. Twenty-eight patients self-reported on perfect adherence to three or more ARVT drugs. Twenty-four patients returned for the follow-up visit. All patients received counseling regarding medication schedules tailored to their life style, medication interactions, side effects and importance of adherence. Patients also received one or more tools to help with medication intake, i.e., alarm clocks, beepers, pillboxes and written schedules. Viral loads were obtained at baseline and follow-up visits.

Results: At the baseline visit, 7/20 (35%) of experienced patients self-reported perfect adherence. At a follow-up visit, 11/17 (65%) of experienced patients and 5/7 (71%) of naive patients self-reported perfect adherence.

Either an undetectable viral load or at least a 10-fold reduction in viral load was present in all naive patients who reported perfect adherence 5/5 (100%) and in 8/11 (73%) of experienced patients who reported perfect adherence at the follow-up visit.

All naive and experienced patients who reported nonadherence had virologic failure.

Conclusion: Our findings are consistent with prior studies, which demonstrated the association of self-reports of adherence with viral outcome. There is a low rate of adherence (35%) to ARVT in our inner-city patient population at baseline. This figure is lower than that described in previous self-reported adherence studies (53–57%), thus highlighting the need for interventions to increase adherence with complicated antiretroviral regimens, in this patient population. We showed that intervention by a clinical pharmacist within a multidisciplinary team approach increases self-reported adherence to medications and correlates with a reduction in viral load.

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Addendum

The last page in Volume 68, Number 2 (March 2001) should have been numbered page 159.

Dendritic Cells and the Control of Immunity:

Enhancing the Efficiency of Antigen Presentation

Ralph M. Steinman, M.D.

Abstract

Background: Relevant antigens often are known for diseases that involve the immune system. Yet purified antigens by themselves do not control immunity, especially T-cell immunity. For example, many antigens have been defined for HIV-1 and melanoma, but good HIV-1 vaccines and melanoma immune therapies are lacking. Dendritic cells (DCs) are important intermediaries between antigens and better control of the immune system.
Methods: Some properties that allow DCs to control immunity are reviewed, followed by new studies using DCs as adjuvants in humans. An emerging area is then detailed, the special mechanisms whereby DCs enhance the formation of ligands for T-cells, i.e., complexes of major histocompatibility complex (MHC) products and antigenic peptides.
Results: Once criteria were developed to identify and isolate DCs, several functional properties became evident. DCs are unusually potent in initiating T-cell mediated immunity in culture. *In vivo*, DCs are positioned to capture antigens and migrate to T-cell areas of lymphoid organs. There, DCs are able to prime animals, controlling the MHC restriction of the primed T-cells and inducing resistance to pathogens. DCs pulsed *ex vivo* with antigens are now being used to induce and expand T-cell immunity in humans. To optimize their use, two areas of DC function need to be harnessed: their terminal differentiation or maturation, and antigen uptake. DCs capture most types of antigens at an immature stage of development, but the cells must receive additional stimuli prior to acquiring potent T-cell stimulatory activity. Stimuli from microbes, inflammation and trauma mature DCs. These change the DCs in several ways, even inducing the formation of MHC II-peptide complexes or T-cell receptor (TCR) ligands. The latter move to the surface in nonlysosomal vesicles that simultaneously carry CD86 costimulatory molecules for T-cell activation. Both MHC and CD86 remain co-clustered in patches at the DC surface. DCs also express a receptor, DEC-205, that enhances antigen uptake and presentation. DEC-205 recycles in an unusual manner through MHC class II-rich, late endosomes or lysosomes, dramatically increasing the presentation of bound ligands. Additionally and importantly, DCs can process dying cells and immune complexes onto MHC class I products, events that are termed the "exogenous pathway" or "cross presentation."
Conclusions: The control of the immune system by DCs reflects numerous specializations, not a single "magic bullet." These specializations include a number of mechanisms that increase the efficiency of antigen uptake and MHC-peptide complex formation. The harnessing of these and other features of DCs provides opportunities for improving immune-based therapies and vaccine design.
Key Words: Dendritic cells, T-cells, antigen presentation, antigen processing, immune therapy, adsorptive endocytosis, cross presentation, costimulators.

Introduction: Antigens Alone, Even Most Preprocessed Antigens, Do Not Elicit Strong T-cell Immunity

To introduce the function of dendritic cells (DCs), consider two situations where disease and the immune system intertwine. For a tumor like melanoma or a chronic virus infection like HIV-1, there is extensive information on the antigens that T-cells can recognize. However, it is still not feasible to use these antigens to induce strong T-cell mediated immunity in patients and then assess if this increases resistance to tumors and viruses. Likewise in transplantation and autoimmunity, where one wishes to dampen the immune response, antigens are known but the immune system cannot be tolerized. What is the obstacle? The obstacle is that antigens alone, even preprocessed peptides that bind to antigen presenting major

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histocompatibility complex (MHC) class I and II products, are insufficient by themselves to regulate T-cell mediated immunity. This obstacle can be addressed by learning to access and activate DCs, a physiologic system for controlling immunity.

DCs were discovered in an attempt to understand immune priming. Dr. Zanvil Cohn and I were trying to explain a need for non-lymphocytes in a test tube system where sheep red blood cells induced a primary, T-cell dependent, antibody response (1, 2). Dr. Kayo Inaba in Kyoto was also interested in the identical problem (3). Together we found that the required accessories for antibody responses were stellate cells that had not been recognized and characterized before (4, 5). These cells (DCs) were found to have many properties that had not been anticipated: potency in inducing T-cell responses, positioning *in vivo* to capture antigens and migrate to lymphoid tissues, and a capacity to prime CD4 and CD8 types of immunity.

One of the key functions of an accessory cell is antigen uptake and processing to form complexes of MHC products and antigenic peptides. MHC-peptide complexes are the ligands for T-cells. Nevertheless, in much of the early experimentation on DCs, the T-cell stimuli that were used did not require antigen processing, e.g., major transplantation antigens (6, 7), mitogens (8, 9), and contact allergens (10, 11). Therefore, it was assumed that the control of immunity by DCs reflected: (a) their accessory or costimulatory properties, where "costimulation" refers to adhesion and activating molecules that work together with MHC-peptide complexes to activate the T-cell, and (b) *in vivo* functions governing DC position and movement. Recent observations, to be summarized here, now show that DCs are additionally specialized to enhance the efficiency of antigen uptake, processing, and presentation on MHC class I and II products. Other new areas of DC research are not mentioned here. These involve the capacity of DCs to influence Th1/Th2 phase differentiation and tolerance, and other immune cells like B cells, natural killer (NK) and NK-T-cells.

Some Features Indicating Important Roles for DCs in the Control of Immunity

Potency. Once DCs were purified, it became evident that they were unusually potent in triggering T-cell clonal expansion and effector function, e.g., CD8+ cytolytic T lymphocytes and CD4+ helper cells. Small numbers of DCs, and relatively small amounts of antigen, were able to stimulate strong T-cell responses in culture. The basis for this potency is not adequately understood, but two features have recently been reported. One is the selective expression by DCs of a lectin, DC-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN), which binds to intracellular adhesion molecule (ICAM)-3 on resting T-cells and enhances the DC-T-cell interaction (12). A second, to be discussed more below, is that the CD86 costimulatory molecule is not only abundant on DCs (13) but also associates with antigen-presenting MHC products in stable patches on the DC surface (14). Therefore, DCs have a specialized T-cell binding molecule, DC-SIGN, and can deliver the key signals for T-cells — MHC and CD86 — in concert.

Position. *In vivo* DCs found in the tissues like the skin and airways are positioned to capture antigens. Also DCs can migrate to lymphoid tissues, via lymphatics primarily, to enter the T-cell areas. There, antigen-bearing DCs are ideally located to select antigen-reactive T-cells from the recirculating pool of lymphocytes, after which the immune response can begin (15, 16).

Priming. DCs are able to initiate immunity from resting T-cells. The activated T-cells are "MHC-restricted," i.e., the T-cells recognize antigen in the context of the MHC haplotype of the priming DCs and respond vigorously to antigens presented by these MHC products expressed on other cells (5, 17). In other words, immune responses develop in two stages: an afferent or priming stage that is controlled by DCs, and an efferent stage that eliminates the antigen via other antigen presenting cells like macrophages and B cells. Mature DCs seem to lack many effector or antigen-eliminating functions, such as the capacity to kill microorganisms or make antibodies. Instead DCs activate T-cells, which then turn on other antigen presenting cells, like B cells and macrophages, to eliminate antigens.

Similar events likely transpire *in vivo* (Fig. 1). DCs can be pulsed *ex vivo* with antigens and then reinfused to autologous or syngeneic recipients (18). T-cells are then activated in the T areas. Next, the activated T-cells or T "blasts" leave the lymph node via efferent lymphatics, enter the blood, and finally the inflammatory site where antigen was initially deposited. The use of DCs as adjuvants in mice results in protective immunity against infections (19) and tu-

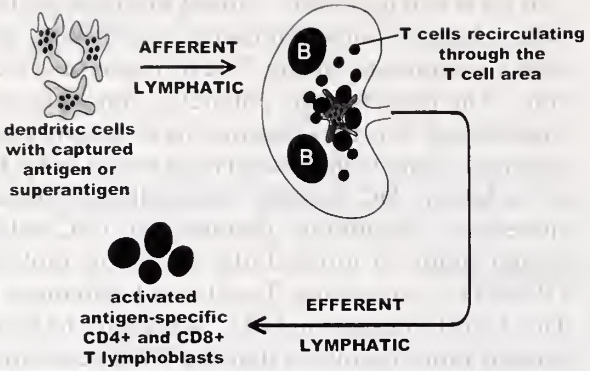
AFFERENT
LYMPHATIC
dendritic cells with captured antigen or superantigen
B
B
T cells recirculating through the T cell area
activated antigen-specific CD4+ and CD8+ T lymphoblasts
EFFERENT
LYMPHATIC

Fig. 1. Two stages of T-cell immunity *in vivo*, the afferent and efferent limbs. In the afferent limb, antigen is picked up by dendritic cells (DCs) that travel to T-cell areas of lymphoid organs, e.g., via afferent lymphatics to the lymph node diagrammed here. In the T-cell areas, DCs select appropriate clones of recirculating T-cells and initiate T-cell expansion and differentiation. Activated T "blasts" leave the lymphoid tissue via efferent lymphatics, enter the blood, and return to the initial inflammatory site to carry out the efferent limb of T-cell immunity together with other antigen presenting cells.

mors (20), but if DCs are carrying an autoantigen, autoimmunity can result (21).

Using Dendritic Cells as Adjuvants in Humans

Given the information in the previous section, it is now feasible to start thinking about the issues posed at the beginning of this article. Can one use DCs to induce stronger immunity to virus infections and tumors in humans? This is a vigorous research area (22, 23) and not simply a matter of "translation" of existing knowledge from mouse to man. More often, key findings in DC biology are being made with humans before being "translated" back into the mouse.

A key obstacle to human DC research has been overcome, at least in part. This is the preparation of large numbers of DCs for purposes of vaccination. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a critical cytokine, being used to expand DCs from proliferating progenitors (24, 25), and for differentiating DCs from nonproliferating monocyte precursors (26, 27). The first successful immunization studies with monocyte-derived DCs, loaded *ex vivo* with antigens, expand CD4+ and CD8+ T-cell immunity upon reinfusion *in vivo* (28, 29). Likewise CD34-derived DCs have been used to expand immunity to melanoma antigens in patients with advanced cancer (30).

There are many ways in which this DC-based, active-immunization approach can be improved. It may be necessary to select for certain types of DCs or specific stages of development. More mature DCs are more immunogenic in mice (31) and in humans (32). It may be important to prolong the life span of the DC (e.g., by treatment with CD40L or TRANCE), since normally most DCs in an injected inoculum do not survive more than 2 days (33). Methods for loading DCs with antigens also need research. It would seem important to load the DCs with multiple epitopes, and on several types of antigen presenting molecules (including MHC class I and class II products), to induce helper and killer cells for many tumor epitopes. Finally, one needs to be able to measure immunity to be able to optimize the use of any adjuvant. The measurement of the human immune response is becoming increasingly quantitative, e.g., through the use of fluorescent-activated cell sorting (FACS) approaches that measure MHC-tetramer-binding and cytokine-producing T-cells.

Specializations of DCs in Converting Antigens into Immunogens

The Concept of DC Maturation. The terminal stage of DC differentiation, prior to death by apoptosis, is a cell that expresses very high levels of antigen presenting MHC products as well as the accessory or costimulatory molecules for T-cell binding and activation. These mature cells arise from immature precursors which, importantly, are the cells that exhibit endocytic activity (Fig. 2). Endocytosis occurs via several pathways: fluid phase pinocytosis including macropinocytosis (34); receptor-mediated uptake via Fc receptors and lectins like the macrophage mannose receptor (MMR) (34); and phagocytosis of microbes and dying cells (35–37) (Fig. 2). In other words, many populations of DCs separate in time their two main functions: antigen capture as immature cells and immune stimulation as mature DCs.

Maturation is, therefore, a critical control point in the initiation immunity. It can be mediated by inflammatory cytokines (interleukin-1 [IL-1], tumor necrosis factor [TNF]), T-cell products (CD40L), microbial constituents (lipopolysaccharide [LPS], CpG oligonucleotides), and trauma (necrosis, transplantation). Maturation leads to the development of many features critical for priming, not just costimulators. For example, maturing DCs produce IL-12, resist immunosuppression by IL-10, and express different chemokine receptors to

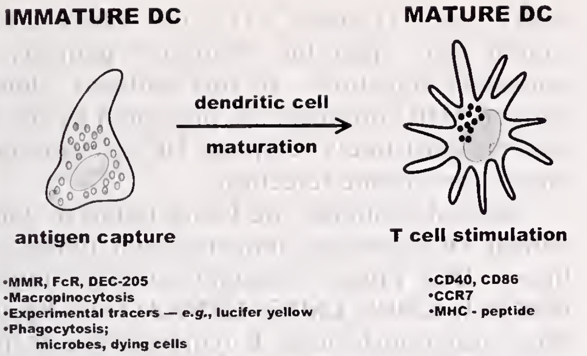

Fig. 2. Dendritic cell maturation, a key control point linking innate and adaptive immunity. Immature DCs are active in endocytosis. There are several adsorptive endocytosis receptors like the MMR, FcR and DEC-205, and DCs that can take up large amounts of substrates (including experimental tracers) by macropinocytosis and phagocytosis. Many stimuli can drive differentiation to form mature or T-cell stimulatory DCs. The stimuli include microbial products (LPS and dsRNA); CpG deoxyoligonucleotides; TNF family members including CD40L on activated T-cells, platelets, mast-cells; and trauma (necrosis and transplantation). Maturing DCs produce large amounts of IL-12 and, in some cases, type I interferons and become specialized in many ways to stimulate T-cells. For example, mature DCs have high levels of T-cell interaction molecules like CD40 and CD86, an important chemokine receptor CCR7, and high levels of MHC-peptide complexes or TCR ligands.

orchestrate their movements and interactions with lymphocytes *in vivo*.

In the past 2 years, it has become apparent that immature DCs are not just "transient phagocytes." Instead they have some unusual ways to enhance antigen uptake and formation of immunogenic MHC-peptide complexes or T-cell receptor (TCR) ligands. Several of these mechanisms are now considered.

The DEC-205 Multilectin Receptor. Monocyte-derived DCs can express two homologous adsorptive endocytosis receptors, the MMR and DEC-205, with 8 and 10 contiguous C-type lectin domains respectively. Natural ligands for the MMR and DEC-205 on DCs are at this time insufficiently characterized. Nonetheless, in spite of sequence similarities whereby both molecules display many contiguous C-type lectin domains, the MMR and DEC-205 can be quite different biologically. In particular, the receptors are found in different intracellular sites within developing mouse DCs (38). As expected, the MMR is abundant within peripheral early endosomes, through which most adsorptive endocytosis receptors recycle. In contrast, DEC-205 is abundant in late endosomes or lysosomes, which in DCs are rich in antigen presenting MHC class II products. These MHC II compartments (MIICs) are the sites in which peptides, formed during lysosomal proteolysis, bind to MHC II molecules prior to exit to the cell surface (14, 31).

To understand the contrasting intracellular distribution of MMR and DEC-205, Karsten Mahnke engineered the cytosolic domains of the MMR and DEC-205 together with the external domains of human CD16. Following transfection into L cells, he could then study the trafficking that is mediated by each tail, and mutants thereof, in the absence or presence of human Ig as ligand (38). Mahnke et al. found that the MMR "tail" trafficked CD16 through early endosomes, whereas the DEC-205 cytosolic domain trafficked CD16 through late endosomes or lysosomes identified with the marker, LAMP, or lysosome-associated-membrane protein (Fig. 3). In both cases, the MMR and DEC-205 tails returned the CD16 to the cell surface to pick up more ligand, human Ig. In the DCs and L cells that we studied, the compartments targeted by DEC-205 also were rich in MIIC products. This feature of an endocytic receptor, i.e., recycling through late endosomes and lysosomes (Fig. 3), has not been seen before.

When aggregated human Ig or Ig-anti Ig immune complexes were next tested as antigens for T-cells primed to human Ig, the L cells that expressed CD16-DEC-205 presented antigen 100 times more efficiently than L cells expressing CD16-MMR. An acidic EDE sequence in the distal part of the DEC-205 tail was critical,

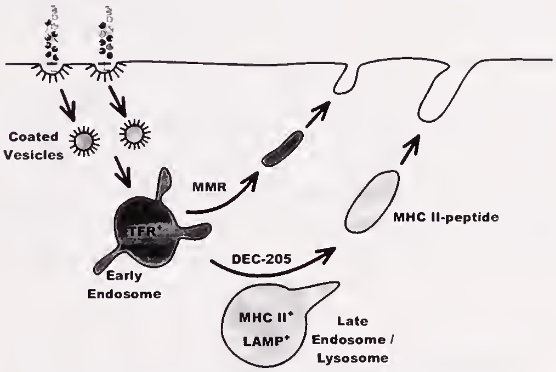

Fig. 3. Distinct intracellular trafficking mediated by the cytosolic domains or "tails" of the MMR (macrophage mannose receptor) and DEC-205 adsorptive endocytosis receptors. The MMR tail, when hooked to the external domains of a human CD16 Fc receptor, recycles CD16 into and out of the cell through early endosomes. This pathway is typical for adsorptive endocytosis receptors, as first noted with low-density lipoprotein receptors. DEC-205, in contrast, traffics via late endosomes or lysosomes, marked by LAMP (lysosome-associated-membrane proteins), that importantly, are rich in MHC class II. This greatly enhances the efficiency of antigen presentation via the DEC-205 cytosolic domain. TFR+ = transferrin receptor.

both for targeting CD16 to MHC II and LAMP-positive compartments and for enhancing antigen presentation.

The Exogenous Pathway for Presentation on MHC Class I. In most antigen-presenting cells, a tiny fraction of endocytosed substrates can be processed into peptides that bind to MHC class II but not to MHC class I. For MHC class I-peptide complexes to form, the peptides are derived from newly synthesized or "endogenous" proteins in the cytoplasm, which are processed via the proteasome and transported into the endoplasmic reticulum (ER) via transporters for antigen processing (TAP). However, the laboratories of Nina Bhardwaj (36, 39) and Sebastian Amigorena (40, 41) have shown that DCs do efficiently present "exogenous" substrates from dying cells and immune complexes onto MHC class I (Fig. 4). Presentation has been shown to be TAP-dependent in the case of immune complexes. Somehow, DCs are able to deliver endocytosed proteins, not just *de novo* synthesized proteins, into the MHC I pathway. The pathway is also called "cross presentation" (cross priming and cross tolerance) because antigens from dying cells of one MHC haplotype can be presented by different MHC molecules expressed by DCs.

Importantly, cross presentation of dying cells is also very efficient for MHC II products on DCs (37, 42). We studied the capacity of mouse DCs to present a peptide derived from I-E MHC II products in dying B cells. If we fed recipient DCs dying B cells, the donor I-E peptide gained access to the MHC II of the DCs more than 1000-fold more efficiently than preprocessed I-E peptide. In other words, when DCs are feeding on dying cells, they should efficiently generate MHC II-restricted CD4 helper cells, whereas the administration of preprocessed peptide will be much less effective. Since the peptide we studied derived from MHC class II itself (37), our observations should bear upon the "indirect" pathway of transplant rejection. In this pathway, donor-derived MHC products are presented by the recipient, most likely recipient DCs, setting up a means for chronic rejection.

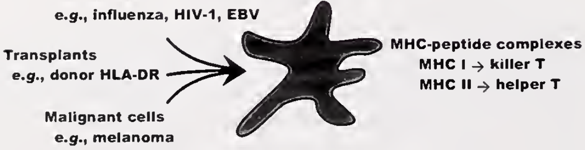

Fig. 4. Dendritic cell presentation of dead and dying cells from various sources to form MHC class I and class II-peptide complexes. This pathway is likely to be very important clinically, because it allows DCs to process antigens from cells that are dying within infectious foci, transplants and tumors. DCs are quantitatively and perhaps qualitatively distinct in their capacity to form TCR ligands by the exogenous pathway.

Several examples are being found in which human DCs process antigens from tumor cell lines. DCs process essential latency antigens (EBNA1, LMP1, LMP2, EBNA3) from Epstein Barr virus-transformed, B-lymphocyte cell lines onto MHC class II (42, 43). Likewise, DCs process antigenic peptides from melanoma cell lines, for presentation on MHC class I and priming of the T-cell response, even with T-cells from patients with advanced melanoma (44). Clinical studies will eventually determine if the delivery of dead autologous or allogeneic tumor cells to DCs, followed by reinfusion, provides a means to immunize a patient to an array of tumor antigens on both MHC class I and class II.

In summary, the capacity of DCs to process dying cells is deservedly drawing enormous attention. It may lie at the heart of many challenging problems in medicine: the indirect pathway of transplant rejection, self-tolerance initiated via presentation of dying self-tissues, immunity to viral and bacteria-infected cells that undergo cell death, and tumor immunity (Fig. 4).

Regulating Antigen Presentation during DC Maturation. Protein entry into the endocytic system is typically followed by presentation of at least some processed peptides on MHC II. However, a fascinating form of regulation of antigen processing and presentation has been found when DCs internalize the protein Hen Egg Lysozyme (HEL) into their lysosomal MIICs. These MHC II-rich compartments are called lysosomes (late endosome might prove to be a more accurate term for these vesicles) because they stain brightly for lysosome-associated membrane proteins or LAMPs and for the peptide-editing MHC product, H-2M or HLA-DM.

Using the C4H3 monoclonal antibody specific for an epitope formed by the complex of HEL peptide and MHC II, we looked for sites of MHC-peptide or TCR-ligand formation in DCs from mouse bone marrow (31). We found that immature DCs endocytosed the HEL into MIICs, as expected, but the cells had to receive a maturation stimulus to form large amounts of C4H3 epitope, i.e., MHC II-peptide complex. This was a nice demonstration that complexes are first found within deep endocytic compartments as suspected, but surprisingly, the formation of MHC-peptide complexes was not simply a matter of delivering antigen to MIICs. Instead, the formation of TCR ligands was maturation stimulus-dependent and could take place if the stimulus was delivered days after entry into the MIIC. Therefore, the endocytic system of immature DCs is not an obligatory site for protein digestion and TCR ligand formation; both seem to be regulated in some way.

Dr. Ira Mellman and his colleagues have found that one level of regulation is very likely at the level of proteolytic activity. The MIICs of immature DCs contain abundant cystatin C, a cysteine protease inhibitor that blocks the function of cathepsin S (45). The latter is critical for invariant chain proteolysis, allowing antigenic peptides to exchange in the MHC II peptide-binding groove with the class II-associated invariant chain peptide (CLIP) fragment of the invariant chain. Accordingly, preprocessed peptides should load the MHC II products of DCs well when a maturation stimulus is also administered; this was indeed observed by Inaba et al. (31).

Maturing DCs also exhibit a beautiful mechanism for the transport of MHC-peptide complexes to the cell surface (14). Following their formation in MIICs, the MHC-peptide complexes are found in abundance in peripheral, nonlysosomal compartments. These vacuoles do not accept most endocytic tracers and rather seem to be transport vesicles, bringing TCR ligands from late endosomes to the cell surface and leaving behind residual endocytosed proteins, HLA-DM, and LAMPs. The term immunogenic "TCR ligand" is really appropriate for the content of these vesicles, because both MHC I and II are abundant, as are the costimulator molecule B7-2 or CD86. Subsequently, at the cell surface the DCs display large amounts of MHC and CD86 ("signals one and two" for T-cell activation) together. This would also allow the DC to set up the immunologic synapse in responding T-cells. The idea of the synapse is that the TCR must cluster to signal well, and that in addition costimulators like CD86 must be juxtaposed to function optimally. If so, DCs that have picked up antigens in the presence of a maturation stimulus are able to display the processed antigens and other T-cell activation signals in a manner that is prone to synapse formation.

Discussion

Successful manipulation of the immune system in the context of many diseases will require, I think, successful manipulation of DCs. Well-defined antigens, coupled with current artificial adjuvants, exhibit poor efficacy. Logically, one should optimize the form of antigen, so that it targets to DCs and efficiently charges antigen-presenting molecules like MHC I and II. Lectin receptors, Fc receptors, and receptors for dying cells all could be valuable in this regard. Then one must mobilize and mature the DC, but do this in concert with antigen uptake. In this way, many elegant features come together at the level of the DC. These include the successful processing of antigens and display of MHC-peptide complexes, and the expression of many other ligands and receptors that orchestrate interactions with T-cells, especially *in vivo*.

We have concentrated on immunogenicity, the clonal expansion and priming of effector T-cells, taking the lead from the melanoma and HIV-1 examples mentioned initially. However, the function of DCs extends beyond this traditional emphasis. DCs can stimulate other types of lymphocytes (e.g., B cells, NK cells, NK-T-cells), and different forms of innate and adaptive (Th1/Th2, tolerance) immunity. Therefore, by learning to manipulate DCs *in vivo*, it should be possible to control many components of the immune response. Additional research on DCs will allow nature's adjuvants to carry out the physiology for which they are beautifully designed.

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Grand Rounds

Coronary Artery Disease:

Pathogenesis and Acute Coronary Syndromes

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Abstract

Atherosclerotic diseases and their thrombotic complications remain the leading causes of mortality and morbidity in Western society. In the United States, cardiovascular disease is responsible for one in every 2.4 (41.4%) deaths and is the leading single cause of mortality. Furthermore, the presence of atherosclerotic disease (defined as thickening of the arterial wall through the accumulation of lipids, macrophages, T-lymphocytes, smooth muscle cells, extracellular matrix, calcium and necrotic debris) is more prevalent, but by itself rarely fatal. The crucial, final common process for the conversion of a nonocclusive, often clinically silent atherosclerotic lesion to a potentially fatal condition is often plaque disruption. The mortality associated with atherosclerotic disease relates to the acute coronary syndromes, including acute myocardial infarction, unstable angina pectoris and sudden cardiac death. Substantial clinical, experimental and postmortem evidence demonstrates the central role that a superimposed acute thrombosis on a disrupted atherosclerotic plaque plays in the onset of acute coronary syndromes. Therefore, therapeutic approaches to date have focused on reducing such thrombotic complications of atherosclerotic plaques (i.e., antiplatelet, anticoagulant and thrombolytic therapies) to reduce the resulting morbidity and mortality.

In this review, we will focus on the current theories of atherogenesis and how they impact on our understanding of acute coronary syndromes.

Key Words: Atherogenesis, atherosclerosis, platelets, platelet aggregation, thrombogenicity, thrombosis, acute coronary syndrome, plaque formation, plaque disruption, hemodynamics, Q-wave myocardial infarction, rheology, collateral circulation, risk factors.

Atherogenesis: The Early Stages

Progression and Classification of Atherosclerotic Lesions

Pathological studies have provided insights into the early changes within the artery wall that may be associated with atherosclerosis. The earliest findings noted were of eccentric intimal thickening in arterial regions opposite the flow divider of arterial bifurcations. The earliest signs of lipid retention were isolated foam cells (macrophages) found within the intima of 45% of infants (1). By puberty, such foam cell accumulations were accompanied by lipid droplets both extracellularly and within smooth muscle cells. These early lesions are the so-called fatty streaks, noted in 65% of children between 12 and 14 years of age. By the third decade of life, these lesions had developed a cap of smooth muscle cells and collagen, thus forming a fibroatheroma. The formation of these fibrous caps is generally slow. However, they may thicken rapidly with the deposition of platelets and fibrin on their surfaces because of thrombus-dependent fibrotic organization.

Based on the above pathological data, atherosclerotic plaque progression was subdivided into five phases and lesion types (Fig. 1) by the American Heart Association Committee on Vascular Lesions (1). Although not severely stenotic by coronary angiography, type IV and type Va lesions are particularly important because they are more susceptible or "vulnerable" to disruption and subsequent thrombosis. Type

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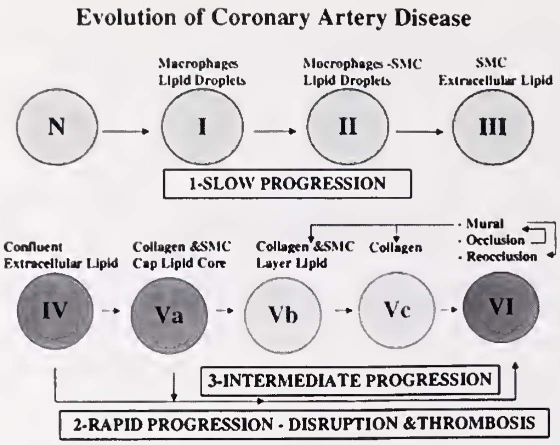
Evolution of Coronary Artery Disease
Macrophages Lipid Droplets
Macrophages -SMC Lipid Droplets
SMC Extracellular Lipid
N
I
II
III
1-SLOW PROGRESSION
Confluent Extracellular Lipid
Collagen &SMC Cap Lipid Core
Collagen &SMC Layer Lipid
Collagen
- Mural
- Occlusion
- Reocclusion
IV
Va
Vb
Vc
VI
3-INTERMEDIATE PROGRESSION
2-RAPID PROGRESSION - DISRUPTION &THROMBOSIS

Fig. 1. Schematic representation of atherosclerotic lesion progression. The solid dark circles indicate those phases where plaque disruption and subsequent thrombosis play a critical role. (taken from ref. #105)

IV lesions have a high extracellular lipid content intermixed with fibrous tissue beneath a fibrous cap. In contrast, type Va lesions contain a larger lipid-rich core with a thin fibrous cap. Upon disruption, these minimally stenotic coronary lesions may lead to acute occlusive thrombosis associated with the acute coronary syndromes or a small nonocclusive thrombus. The latter event may lead to a severe stenotic lesion after fibrous organization within the underlying atherosclerotic plaque. This abrupt episodic progression of disrupted "vulnerable" plaques leads to the frequent complicated type VI lesion that accounts for about 75% of the patients with acute coronary syndromes.

Importance of Rheology, Endothelial Dysfunction and Inflammation in Early Atherosclerosis

The arterial vessel wall and the endothelial cells are subject to mechanical and hydrostatic forces exerted by blood within the vessel, circumferential stress from motion of the vessel during the cardiac cycle and shear stress resulting from blood flow within the vessel. The biological implication of these mechanical forces is clearly demonstrated by the preferential localization of atherosclerotic lesions at certain sites within the arterial tree despite the presence of the same systemic, genetic and environmental factors. It is the last of these forces, shear stress, which appears to have the greatest impact upon events occurring at the interface of the blood and vessel wall. Shear stress stimulates the release of vasoactive substances, and changes such cellular processes as gene expression (i.e., via shear-stress-responsive elements), cell metabolism and cell morphology (2, 3). At areas of abrupt curvature in the vessel (such as at the carotid bulb), laminar blood flow is disrupted, which results in recirculation vortices and low mean shear stress and flow reversal. The correlation is strong between endothelial dysfunction and areas of low mean shear stress and oscillatory flow with flow reversal (4). The predilection of the endothelial cell surface at these sites for cellular adhesion molecules, increased uptake of lipoproteins, inflammatory cell transmigration, and the secretion of chemokines and cytokines leads to the proliferation of smooth muscle cells and macrophages within the vessel wall. Thus, high mean shear stress inhibits leukocyte binding and chemokine and cytokine expression, while low mean shear stress promotes inflammatory cell binding.

The endothelium plays a central role in arterial hemostasis through the regulation of plasma lipoprotein permeability and leukocyte adhesion, and the production of prothrombotic and antithrombotic factors, growth factors and vasoactive substances (Fig. 2). There is substantial data demonstrating that shear stress is an important stimulus for the secretion of prostacyclin (5, 6) and nitric oxide (NO) (7–9), both of which are potent inhibitors of platelet aggregation. Furthermore, shear stress has been shown

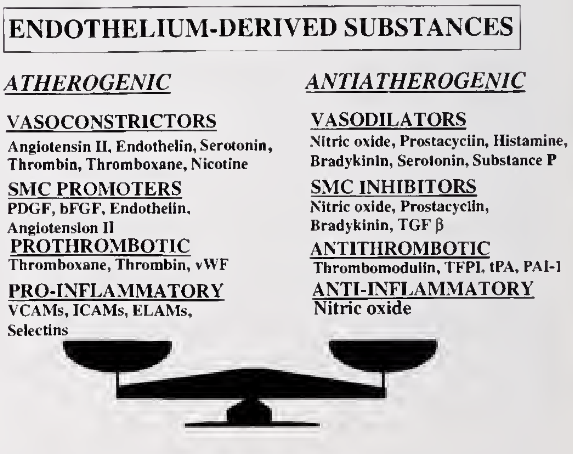
ENDOTHELIUM-DERIVED SUBSTANCES
ATHEROGENIC
VASOCONSTRICTORS
Angiotensin II, Endothelin, Serotonin, Thrombin, Thromboxane, Nicotine
SMC PROMOTERS
PDGF, bFGF, Endothelin, Angiotension II
PROTHROMBOTIC
Thromboxane, Thrombin, vWF
PRO-INFLAMMATORY
VCAMs, ICAMs, ELAMs, Selectins
ANTIATHEROGENIC
VASODILATORS
Nitric oxide, Prostacyclin, Histamine, Bradykinin, Serotonin, Substance P
SMC INHIBITORS
Nitric oxide, Prostacyclin, Bradykinin, TGF β
ANTITHROMBOTIC
Thrombomodulin, TFPI, tPA, PAI-1
ANTI-INFLAMMATORY
Nitric oxide

Fig. 2. Endothelium-derived substances. Note the list of pro- and anti-atherogenic factors that could be produced by the endothelium (see text). **PDGF.** -Platelet Derived Growth Factor; **bFGF.** -basic Fibroblast Growth Factor; **VCAM.** -Vascular Adhesion molecules; **ICAM.** - Intercellular Adhesion Molecules; **ELAM.** -Endothelial Leukocyte Adhesion Molecule; **TGF-β.** - Transforming Growth Factor Beta; **TFPI.** -Tissue Factor Pathway Inhibitor; **tPA.** -tissue-type Plasminogen Activator; **PAI-1.** -Plasminogen Activator Inhibitor-1; **vWF.** -von Willebrand factor.

to regulate the production of thrombomodulin (10), which (through interaction with proteins C and S) inactivates specific clotting factors, stimulates the expression of tissue plasminogen activator (10 – 12) and reduces the secretion of plasminogen activator inhibitor type 1 (12), thus promoting fibrinolysis as well. The genes for the production of tissue factor, one of the most potent stimuli for thrombin generation via the extrinsic pathway of the coagulation cascade, are upregulated in conditions of low mean shear stress (13), and promote the existence of a prothrombotic endothelial surface. Thus, in conditions of low mean shear stress, anticoagulant mechanisms are inhibited, in contrast to the activation of procoagulant pathways.

Recruitment of monocytes into the vessel wall is an early step in the formation of an atherosclerotic lesion. The fatty streak, the precursor for atherosclerotic lesions, contains macrophages and T lymphocytes exclusively (1), although the deposition of lipids precedes this inflammatory cellular influx in patients with hypercholesterolemia (14, 15). The subsequent migration of leukocytes across the endothelium depends on chemotactic factors such as monocyte chemoattractant protein 1 (MCP-1) and oxidized low density lipoproteins (LDL) (16) as well as platelet-endothelial cell adhesion molecules (17). Substances such as monocyte colony stimulating factor seem important for the survival and multiplication of macrophages within the growing atherosclerotic lesions (18, 19). T-cells are similarly dependent on interleukin-2 (20). Macrophages produce many growth factors (including platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and epidermal growth factor (EGF), in addition to the inflammatory agents described above (21). However, it is the production of matrix-degrading substances (matrix metalloproteinases (MMP) and heparanases) which are crucial to the perpetuation and growth of the early lesion (22). Gelatinase A (MMP-2) degrades the collagen found in the basement membranes, and appears to be critical in facilitating smooth muscle migration through the basement membrane (23). The major control of MMP activity, once activated from the inactive zymogen, lies with the production of tissue inhibitors of MMPs (TIMPs) (22), of which three have been identified to date. It appears that the ratio of MMPs to TIMPs is crucial in determining connective tissue and basement membrane breakdown. Lymphocytes, including CD4 and CD8 positive T-cells, have been identified in significant numbers within atherosclerotic lesions, and invariably play a role in the inflammatory processes in plaque genesis and progression (24, 25). These T-cells are activated when they bind antigens processed and presented by both macrophages and smooth muscle cells. One such antigen may be oxidized LDL (26). Smooth muscle cell proliferation, an important feature of atherosclerotic lesions, is stimulated and regulated by endothelial factors, of which shear stress is one (27). Low mean shear stress (which is pro-atherogenic) has been shown to be associated with increased production of endothelial PDGF (27). High mean shear stress (which is anti-atherogenic or atheroprotective) has been associated with reduced production of endothelin-1 (28) and angiotensin II (29), both of which are smooth muscle mitogens, and increased production of NO (30, 31) and transforming growth factor β (TGF-β). These latter two substances are inhibitors of smooth muscle cell growth. Thus, substantial evidence exists for shear stress mediated modulation of vascular smooth muscle cell proliferation.

Platelets and Thrombosis in Early Atherosclerosis and Acute Coronary Syndromes

Platelet deposition and thrombosis atop an atherosclerotic lesion lead to one of two broad events (Fig. 3). First, nonocclusive luminal thrombosis leads to silent, rapid plaque growth.

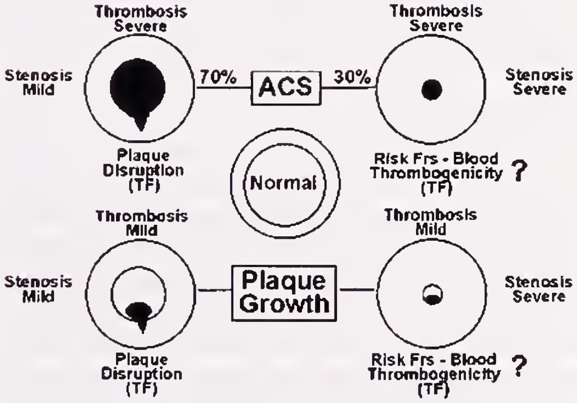

Fig. 3. Diagram showing the various outcomes that result from the thrombotic complications of atherosclerotic disease. Plaque disruption and subsequent thrombosis are associated with 70% of the acute coronary syndromes, while the remaining 30% seem to be caused by the existence of a severe stenosis triggering thrombosis. **ACS.** -Acute Coronary syndromes. The **?** marks refer to the potential effect of a newly reported systemic pool of tissue factor (TF).

During serial angiographic studies, the presence of a mild or moderately stenotic plaque (<50%) was the most frequent cause of acute ischemic events (32–35). These studies also noted that even without clinical symptoms, some minor lesions had progressed rapidly in size over a short period. Postmortem studies of patients dying from ischemic events have revealed the cause of both the acute events and lesion progression to be intimately related to plaque-associated thrombosis (36–41). The atherosclerotic lesions that appeared susceptible or prone to such thrombotic phenomena were noted to have common histological characteristics. These so-called "vulnerable" plaques are more prone to plaque disruption and subsequent thrombus formation.

Second, occlusive (transiently or permanently) luminal thrombosis is associated with unstable angina pectoris, acute myocardial infarction or sudden cardiac death. Plaques containing a large atheromatous core are more prone to disruption, since 75% of such plaques are responsible for the atherothrombotic complications leading to the acute coronary syndromes (42-45). Most of the other cases are associated with plaque thrombosis atop a macrophage-rich intimal erosion in a more fibrotic plaque, often in association with a severe arterial stenosis (42-44).

Plaque Disruption

Plaque disruption is a central feature of atherothrombotic syndromes, and the risk that this will occur relates to the existence of several factors that can be divided into intrinsic (related to plaque composition) and extrinsic (mostly related to the geographical location of the lesion) (Table 1).

Intrinsic Factors

Atherosclerotic plaque disruption generally occurs at sites where the fibrous cap is thinnest and most heavily infiltrated with macrophage-derived foam cells (i.e., its weakest point). This usually is seen at the shoulder region of eccentric lesions (43) (the interface between the normal vessel wall and the atherosclerotic plaque). Factors associated with fibrous cap rupture include size of the atheromatous core (i.e., ratio of lipid to fibrotic components), thickness and composition of the fibrous cap (i.e., ratio of smooth muscle cells to macrophages), inflammation within the fibrous cap and cap fatigue.

While the composition of most atherosclerotic lesions is mainly fibrotic, a significant atheromatous core does exist in most so-called culprit lesions for acute coronary syndromes (46). Several studies confirm the association between size of the atheromatous core and risk for subsequent plaque rupture. One study found that in aortic plaque an atheromatous core of > 40% of the plaque content was at a particularly high risk of disruption and subsequent thrombosis (47). Based on numerous animal studies, lipid-lowering approaches are believed to decrease the lipid content of the plaque (i.e., decrease the size of the lipid-rich core), resulting in a more fibrotic and stable plaque (48–50).

TABLE 1

Determinants of Atherosclerotic Plaque Vulnerability

- **INTRINSIC FACTORS**

COMPOSITION
→ **Lipid vs Fibrotic content**
→ **Cell Population (Macrophages vs SMC)**

- **EXTRINSIC FACTORS**

Circumferential Tensile Stress(moderate stenosis>tension than severe stenosis)
Compressive Stress (vasoconstriction)
Circumferential Bending
Longitudinal flexion stress
Shear stress (laminar vs oscillatory)

Fibrous caps vary widely in their thickness and composition. However, fibrous caps are thinnest at the shoulder regions of the vulnerable plaques (43). Collagen (in particular, type 1 collagen) is a critical determinant of fibrous cap strength. In disrupted aortic plaques, smooth muscle cells (the source of collagen in the cap) and the collagen content itself are decreased (47, 51). One mechanism postulated for the reduced number of smooth muscle cells in the fibrous cap is apoptosis (51). It is uncertain whether this is the only mechanism responsible.

Pathological studies (with immunohistochemistry) have revealed evidence of ongoing inflammation within the fibrous cap at sites of disruption, and other studies have shown macrophage infiltration at the disrupted shoulder regions of fibrous caps (42, 52, 53). An important mechanism appears to be the production of matrix-degrading enzymes, including MMPs, which played an important role in atherogenesis also. Activated macrophages within the fibrous cap produce a variety of MMPs, and *in-vitro* studies have confirmed the ability of these enzymes to degrade fibrous caps (54). Although many of these enzymes have been implicated, including the interstitial collagenases MMP-1 and -3 (55), only gelatinase B (MMP-9) has been associated with rupture-prone areas in human coronary artery specimens obtained at atherectomy (56). T-cells are present in increased numbers at these rupture-prone sites also, and can stimulate macrophages to produce MMP-9 (57).

Extrinsic Factors

Atherosclerotic lesions within the coronary arterial system are subject to mechanical and hemodynamic forces that may trigger disruption of atherosclerotic plaques (58, 59). Cap tension refers to the circumferential wall tension exerted on the vessel due to the blood pressure. This force is governed by Laplace's law; the higher the blood pressure and the larger the luminal diameter, the more tension will develop in the wall (58). The soft atheromatous core is unable to bear these forces well, and the tension is redistributed to adjacent structures such as the fibrous cap (43). Thus, we can appreciate that mildly-to-moderately stenotic lesions will be subject to greater circumferential stresses, in accord with Laplace's law, than severely stenotic lesions. Other forces to which the coronary artery wall and atherosclerotic lesions are subject include longitudinal flexion and circumferential bending associated with the motion of the heart and the propagating pulse wave. It appears that part of the mechanism by which β-blockers exert their favorable effect on reducing reinfarction is by attenuating these forces. Finally, vasospasm and plaque hemorrhage could potentially enhance plaque rupture by compressing the atheromatous core, and cause the plaque to "blow out" into the vessel lumen (53, 60). However, there are little data to confirm the significance of this mechanism in plaque rupture.

Acute Thrombosis

Substrate and Tissue Factor Dependent Thrombosis

Studies of the relative thrombogenicity of the various components of atherosclerotic plaques have demonstrated that lipid-rich plaques are up to six times more thrombogenic than all other components (61). The exact mechanisms for the thrombogenicity of the lipid core are uncertain. However, it has been shown that lipid cores have a high tissue factor content (62), and this may account for some or most of the thrombogenicity (Fig. 4). This tissue factor may originate in macrophage-derived foam cells (63, 64). Studies with directional atherectomy specimens from patients with unstable coronary syndromes showed a higher population of macrophage-rich areas than specimens from stable angina patients. Moreover, there was a significant correlation between these macrophage-rich areas and positive tissue factor staining in atherectomy samples from those patients with unstable coronary syndromes (65–67). Based upon immunohistochemical evidence, it is likely that macrophages are responsible for the bulk of the tissue factor found in the core. This tissue factor may derive from cell debris or microparticles released during apoptosis (68). Plaque disruption may thus expose active tissue factor to circulating blood, leading to acute thrombosis. Furthermore, in models of thrombosis induced by a damaged arterial wall, tissue factor pathway inhibitor (TFPI) has a potent antithrombotic effect (Fig. 5). Despite this evidence, tissue factor in the lipid core may potentially be derived from other sources.

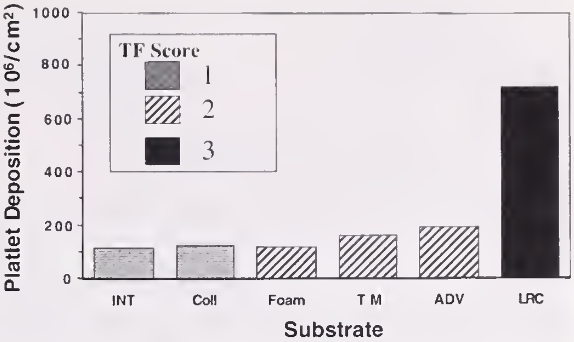

Fig. 4. Platelet deposition and Tissue Factor (TF) activity score in human tissues. Mean values for platelet deposition are illustrated on the ordinate. The intensity of tissue staining is expressed as the average of the scores determined by two independent observers. Note the positive correlation between platelet deposition and TF score on the exposed human substrates. **INT** - normal intima; **Coll** - collagen-rich matrix; **Foam** - foam cell–rich matrix; **TM** - normal tunica media; **ADV** - adventitia; **LRC** - lipid-rich core. Atherosclerotic lesions characterized by the presence of a lipid-rich core (LRC) are most thrombogenic and have the highest content of TF. (taken from ref. #62)

Preliminary evidence is emerging that identifies a plasma source of tissue factor. A modest increase in plasma tissue factor levels (measured by enzyme-linked immunosorbent assay, ELISA) was reported in a study of 31 patients experiencing acute and chronic phases of myocardial infarction versus those with stable angina or controls (69). Tissue factor activity was not measured. In a follow-up study (70), this research group also reported that plasma TF

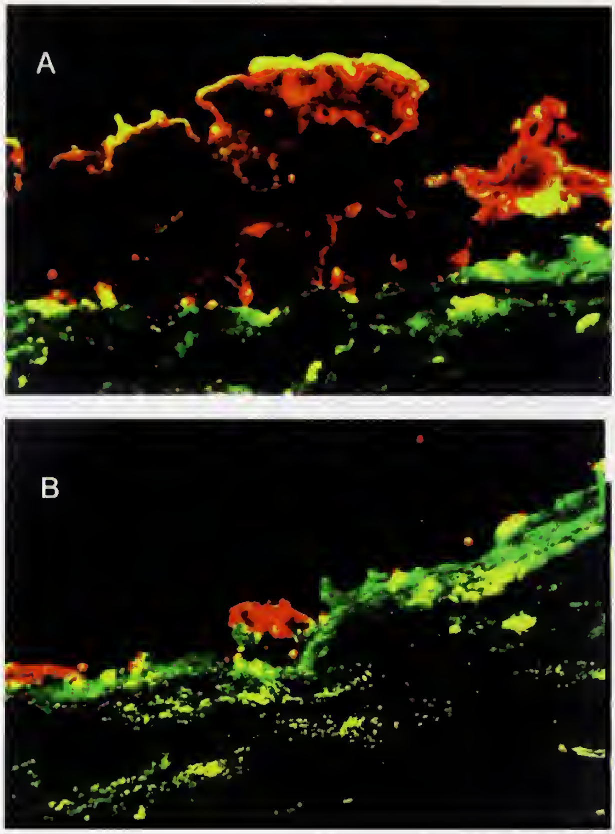

Fig. 5. Effect of the inhibition of TF activity by rTFPI on the thrombogenicity of human atherosclerotic lesions. **A.** Representative immunophotographs of control. **B.** TFPI-treated human lipid-rich atherosclerotic lesions. Fibrin(ogen) deposition is shown as green, platelet deposition as red, and their co-localization as orange. Note significant reduction in both platelet and fibrin(ogen) induced by specific inhibition of TF in atherosclerotic lesions. (taken from ref. #106)

and TFPI levels were increased in the acute and subacute phase of patients with unstable angina and correlated with increases in free TFPI and TF (Fig. 6). Most important, patients with unstable angina and heightened tissue factor were at increased risk for unfavorable outcomes. However, in this study too, tissue factor activity was not measured, nor was the source of the plasma tissue factor addressed.

The source of this circulating tissue factor remains to be determined. Although endothelial cells, macrophages, smooth muscle cells and myocardial cells may be the source of circulating tissue factor, the possibility that this circulating moiety derives, in part, from blood monocytes and/or neutrophils is being actively investigated. Preliminary data by immunoelectron microscopy indicates that tissue factor antigen is most abundant in membrane vesicles that cluster near the surface of platelets (71). More recent

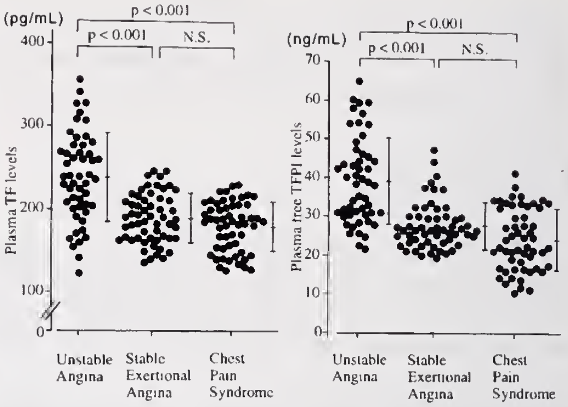

Fig. 6. Evidence of increased tissue factor (TF) and tissue factor pathway inhibitor (TFPI) antigen plasma levels in patients with acute coronary syndromes. Unstable angina patients show higher levels of both TF and TFPI than stable angina or chest pain syndrome patients. (taken from ref. #70)

research has demonstrated tissue factor in monocytes and neutrophils in peripheral blood.

Systemic Thrombogenicity

There is substantial experimental and clinical evidence that a primary hypercoagulable or thrombogenic state that promotes focal thrombus formation may exist in the circulation (Table 2). This is important when considering the risk of complicating thrombosis after plaque rupture and confirms that factors beyond the atherosclerotic plaque are also important in predicting thrombotic risk. Systemic factors, including alterations in lipid and hormonal metabolism, hemostasis, fibrinolysis, and platelet and leukocyte function, are associated with increased blood reactivity and thrombogenicity.

TABLE 2

Factors Modulating Platelet-Arterial Wall Interaction

LOCAL FLUID DYNAMICS
- Shear stress
- Tensile Stress

NATURE OF THE EXPOSED SUBSTRATE
- Degree of injury (mild vs severe arterial injury)
- Composition of atherosclerotic plaque
- Residual mural thrombus

SYSTEMIC THROMBOGENIC FACTORS
- Hypercholesterolemia
- Catecholamines (smoking, cocaine, etc.)
- Smoking
- Diabetes
- Homocysteine
- Lipoprotein (a)
- Infections *(Chlamydia pneumoniae, Helicobacter pylori,* CMV)
- Hypercoagulable state (Fibrinogen, vWF, TF, factor VII)
- Defective fibrinolytic state , etc.

CMV. -Cytomegalovirus. TF.-tissue factor. vWF. -von Willebrand Factor

Increased plasma levels of catecholamines may favor platelet reactivity. Platelet aggregation and the generation of thrombin by circulating catecholamines have been documented experimentally (72–74). It seems probable that this association helps to explain the link between emotional stress (75) and circadian variation (i.e., early morning clustering of events) (76–78) with myocardial infarction. There has been increasing evidence of enhanced platelet reactivity in cigarette smokers (Fig. 7) (79–81); this reactivity may or may not be related to catecholamine levels (82). The enhanced thrombogenicity of smoking is further confirmed by the finding that there is a sharp decline in acute vascular events most often associated with thrombosis when smoking ceases (83, 84).

Hypercholesterolemia has been linked with hypercoagulability (85–87) and enhanced platelet reactivity (88–90) in many studies. Young patients with a strong family history of coronary artery disease seem to have increased platelet reactivity. The hypercoagulable state, associated with hypercholesterolemia, can be reversed with the normalization of lipid levels with lipid-lowering therapy (87, 91).

Homocysteine has been shown to be associated with arterial thrombosis and atherosclerosis. Homocysteine increases tissue factor activity of the endothelial cells, possibly with lipoprotein (a). Homocysteine also inhibits the expression of endothelial cell surface thrombomodulin (the substance central to the activation of protein C), and the binding activity of antithrombin III to the endothelial heparan sulfate. Thus, homocysteine reduces the natural anticoagulant properties of the normal endothelium (92–95).

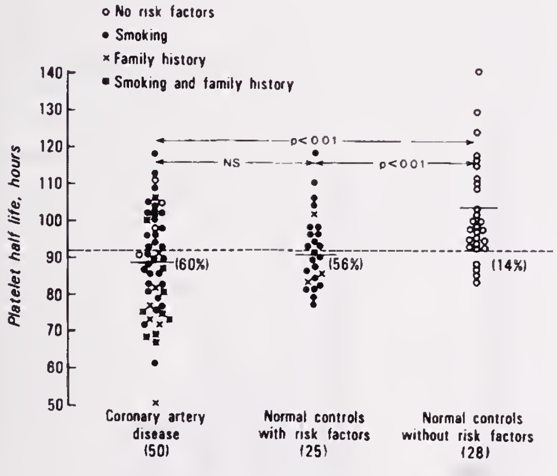

Fig. 7. Effect of smoking and other risk factors on platelet survival. Distribution of platelet survival half-life in three groups of subjects. The absence or presence of cigarette smoking or family history in each subject is indicated. The dashed line (at 92 hours) separates those subjects with a normal platelet half-life (≥92 hours) from those with a shorter platelet half-life. The solid short horizontal line shown for each group denotes the average platelet survival half-life for that group. The percentage of individuals in each group whose platelet half-life survival was less than normal is indicated. The number of individuals in each of the three groups was 50, 25 and 28 respectively. (taken from ref. #80)

It seems clear that defects within the fibrinolytic pathways lead to an increased thrombogenic risk in patients with coronary artery disease (96–98). A correlation between high levels of plasminogen activator inhibitor-1 (PAI-1), tissue-type plasminogen activator (tPA) and crosslinked fibrin with the progression of atherosclerotic disease has been documented (99). Furthermore, it has been shown that in patients with angina pectoris, plasma levels of fibrinogen, von Willebrand factor (vWF) and tPA are independent predictors of subsequent myocardial infarction or sudden death (86). In patients with some types of dyslipidemia, high levels of PAI-1 correlate with the cholesterol levels. While this suggests a potential mechanism by which hypercholesterolemia is associated with increased thrombogenicity, the association between PAI-1 and coronary artery disease and acute myocardial infarction is unclear, with conflicting reports in the literature (86, 100).

Other hemostatic proteins have also been investigated with regard to their role as thrombogenic risk factors. Several prospective studies have indicated that high plasma fibrinogen concentrations are independent risk factors for coronary artery disease and myocardial infarction (101). The mechanism by which fibrinogen contributes to atherogenesis is not well understood. Hypotheses include increased fibrin formation, increased viscosity, platelet aggregation and stimulation of smooth muscle cell proliferation. It is, however, also important to note that high plasma fibrinogen levels correlate with age, degree of obesity, hyperlipidemia, diabetes, smoking, and emotional stress. All of these conditions are associated with atherosclerosis.

Coronary Vasoconstriction

Coronary vasospasm may play an important role in the pathogenesis of acute coronary syndromes, as documented through electrocardiographic and angiographic studies (102). In the setting of a minor plaque disruption with a small thrombotic response, there can still be the release of vasoactive substances by both the platelet and the arterial wall, leading to further compromise of coronary blood flow (103). Coronary artery vasospasm was found to be an important contributor to the phenomenon of intermittent coronary artery occlusion in patients with acute myocardial infarction (104).

Clinical Manifestations of Atherothrombosis

The clinical manifestations of atherosclerotic plaques depend on several factors, including the degree and abruptness of blood flow obstruction, duration of decreased myocardial perfusion, myocardial oxygen demand at the time of the blood flow obstruction, and extent of the thrombotic response to plaque disruption.

Plaque disruption (whether erosion or rupture) may be accompanied by hemorrhage into the plaque and with a variable amount of luminal thrombosis. If the thrombus is small, the plaque disruption probably proceeds unnoticed. If the thrombus is large enough to compromise blood flow through the coronary artery, the individual may experience an acute ischemic syndrome.

Disruption of an atherosclerotic plaque in the coronary arteries, whether ruptured or fissured, plays a fundamental role in the development of the acute coronary syndromes, including unstable angina pectoris, acute myocardial infarction or sudden cardiac death (20, 36, 105, 106). Coronary thrombosis almost exclusively occurs in the setting of underlying atherosclerosis, with disruption of the underlying plaque triggering thrombosis (107). Angioscopic studies have documented the presence of intraluminal thrombi both in unstable angina (108 – 112) and in acute myocardial infarction (111, 113). The incidence of thrombi in unstable angina varied significantly among different studies. These variations were related to the time between anginal symptoms and the angiographic study (110, 114 – 116). The shorter the interval between the two, generally the higher the likelihood of finding occlusive thrombi.

When injury to the vessel wall is minimal, the thrombogenic stimulus is relatively mild. Any resulting thrombotic occlusion is probably transient, as may occur in unstable angina (105, 106). On the other hand, deep vessel injury, as is seen with plaque rupture, results in the exposure of collagen, lipids and other intravascular components, which leads to a more persistent thrombotic occlusion and acute myocardial infarction (107).

Plaque fissuring or rupture with subsequent thrombosis accounts for many episodes of unstable angina or acute myocardial infarction. However, other mechanisms may be important in the etiology of acute coronary syndromes; one such mechanism involves alterations in the balance between myocardial oxygen supply and demand. In patients with stable coronary artery disease, symptoms often result from increases in myocardial oxygen demand. Unstable angina, non-Q-wave and Q-wave myocardial infarction represent a continuum of the same disease process and, in contrast to the setting of stable angina, are usually characterized by an abrupt reduction in coronary artery blood flow (107). In unstable angina, the thrombotic vessel occlusion tends to be transient and episodic, leading to anginal symptoms at rest. In addition to plaque disruption, other mechanisms may contribute to the reduction in coronary flow. As mentioned earlier, platelets that have attached to the disrupted plaque release vasoactive substances including thromboxane A_2 and serotonin, promoting the aggregation of further platelets to the area and inducing vasoconstriction (103). Alterations in perfusion probably account for 60 – 70% of cases of unstable angina. The remainder appears to be mainly due to transient increases in myocardial oxygen demand (117).

In non-Q-wave myocardial infarction, the angiographic morphology of the responsible lesion is similar to that seen in unstable angina, confirming that plaque disruption is common to both syndromes. However, about 25% of patients with non-Q-wave myocardial infarction have a totally occluded, infarct-related artery at early angiography, with the distal myocardium supplied by collateral vessels (107). The presence of ST-segment elevation in the electrocardiogram, the early peak in the plasma creatine kinase and the high angiographic patency rate of the infarct-related artery all suggest that complete coronary occlusion followed by early reperfusion (< two hours) due to resolution (partial or total) of the thrombus and/or of the vasospasm is important in the pathogenesis of most non-Q-wave myocardial infarctions. Thus, limiting the duration of myocardial ischemia by enhancing spontaneous thrombolysis, inhibiting or resolving vasospasm, and promoting a well-developed collateral circulation can prevent the formation of Q-wave myocardial infarction (107).

Deep arterial injury or ulceration results in the formation of a fixed and persistent thrombus leading to the abrupt cessation of myocardial perfusion, and necrosis associated with

Q-wave myocardial infarction (105, 106). The coronary artery lesion responsible for the infarction is frequently only mild to moderately stenotic, suggesting that plaque rupture with subsequent thrombosis is the primary source of the occlusion, rather than the severity of the underlying lesion (Fig. 8) (36). Although an individual severe stenosis has been shown to occlude more frequently than a milder stenosis, the latter accounts for more coronary artery occlusions, due to its much greater frequency (118). Moreover, the milder stenoses are much less likely to be associated with a collateral circulation that might protect against an acute clinical event (119) if an occlusion does occur. In approximately 25% of patients with Q-wave infarction, coronary thrombosis results from superficial intimal injury in association with a high-grade stenosis (105, 106).

The acute onset of malignant ventricular dysrhythmias (ventricular tachycardia and ventricular fibrillation) appears to account for the syndrome of sudden cardiac death in patients with extensive myocardial infarction or cardiomyopathy (120). A malignant ventricular dysrhythmia and sudden cardiac death may also occur with a rapidly progressive coronary artery lesion following plaque rupture and thrombosis in the face of little or no collateral flow and acute myocardial hypoperfusion (120).

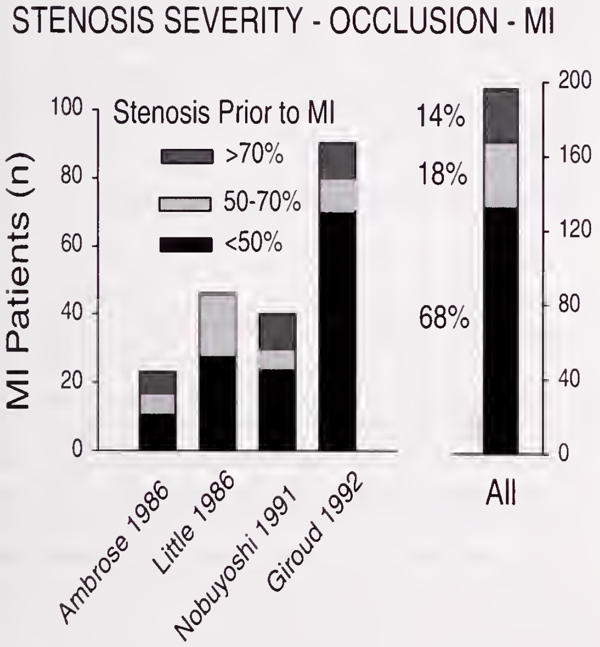

Fig. 8 . Meta-analysis of studies showing the association between stenosis severity and associated risk of coronary occlusion and myocardial infarction (MI). (taken from ref. #36)

Vascular Biology of Risk Factors

Lipoproteins

Elevated low-density lipoprotein (LDL) is associated with endothelial injury and inflammatory responses in the vessel wall (121 – 123). These effects of LDL are especially potent when modified by oxidization or glycation, or associated with immune complexes (121, 124 – 126). Oxidized LDL is avidly taken up by tissue macrophages within the vessel wall, either via LDL receptors (which are subject to down-regulation) or scavenger receptors (which are not subject to feedback mechanisms), leading to the accumulation of cholesterol esters and eventually foam cell formation (127). These foam cells may undergo necrosis due to the direct cytotoxic effects of modified LDL or a process of programmed cell death called apoptosis, induced by certain inflammatory cytokines (20, 128). These two processes lead to the accumulation of extracellular lipid that may coalesce, forming a lipidic, necrotic core.

The density, not just the quantity, of the systemic LDL particles has been shown to correlate with risk of atherosclerotic disease (129). Small, dense LDL particles are more susceptible to peroxidation (130, 131) and thus promote atherogenesis by the mechanisms described above.

Antioxidants have been shown to reduce the size of atherosclerotic lesions (123, 132 – 135) and fatty streaks (135) in animal models. Antioxidants have also been shown to increase the resistance of human LDL to oxidation *ex vivo*, commensurate with the plasma vitamin E levels (136). Although the incidence of myocardial infarction has been reduced by vitamin E supplementation in some preliminary clinical trials, a clear mortality benefit from this therapy has not been shown (137 – 140). Other antioxidants (e.g., β-carotene) appear to have no independent cardiovascular benefits (136, 141, 142).

Triglyceride-rich lipoproteins appear to be important contributors to coronary atherosclerosis. Mechanisms include increased thrombogenicity; small, dense LDLs; postprandial lipidemia with increased chylomicrons and very low density lipoproteins (VLDLs); decreased high-density lipoprotein (HDL) levels; and insulin resistance.

HDL fractions appear to counter the atherogenic effects of LDL, although it is unclear which mechanism(s) is responsible. There may be lipid dependent and independent effects (143). Clearly, the role of HDL in reverse cholesterol transport (the removal of cholesterol from peripheral, extrahepatic sites including the vessel wall and returning it to the liver for metabolism or excretion) can explain some of its atheroprotective effect (143). However, HDL (of which there are discrete subfractions with variable effects) has also been shown to have antioxidant (144) and anti-inflammatory effects (145, 146). In a recent, large-scale clinical trial, therapy specifically directed at elevating the HDL in patients with coronary artery disease and low HDL level was shown to reduce significantly the risk of a major cardiovascular event (147).

Lipoprotein (a) is an independent risk factor for coronary artery disease (148 – 151). Apolipoprotein (a), the major apoprotein found in lipoprotein (a), has close structural homology with plasminogen (152). There is evidence that high levels of lipoprotein (a) result in competitive inhibition of the fibrinolytic activity of plasminogen (153). However, this metabolic condition appears more important in atherogenesis than thrombogenesis (154).

Diabetes

Diabetes is associated with a severely dysfunctional endothelium. Impaired endothelium-dependent relaxation, the best characterized of these abnormalities, can be induced by short exposure to high glucose concentrations. Diabetes may impair endothelium-dependent relaxation by an increased generation of advanced glycosylation end products and increased oxygen free radicals in the arterial wall (155). High glucose levels have also been shown to impair endothelial regeneration (156, 157).

Platelet aggregation and coagulation are increased in diabetes mellitus. Platelets from diabetic patients have shown enhanced adhesiveness and hyperaggregability in response to a wide range of agonists (156, 157). Elevated thromboxane A_2 synthesis occurs in diabetic patients, facilitating platelet aggregation and thrombus formation (158). The primary reason for altered platelet behavior in diabetes is not well understood, but there is evidence that the derangement may start with the megakaryocyte. Other abnormalities in the coagulation system of diabetic patients include increased fibrinogen and vWF levels and decreased antithrombin III activity in response to hyperglycemia. In addition, a typical feature of insulin resistance and hyperinsulinemia is an increased PAI-1 activity, resulting in reduced plasma fibrinolytic activity (159).

Hypertension

One of the mechanisms by which hypertension promotes atherogenesis is through the induction of endothelial dysfunction. Furthermore, hypertension appears to attenuate responses of the vessel wall to endothelium-dependent vasodilators, to increase vascular permeability to macromolecules such as lipoproteins, and to increase endothelin production and inflammatory cell adherence. Hypertension is also associated with phenotypic changes in vascular smooth muscle cells, increasing their proliferative potential and response to growth factors.

Smoking

Smoking is clearly linked to many events known to induce atherosclerosis, including increased fibrinogen levels, enhanced platelet reactivity and increased whole blood viscosity associated with secondary polycythemia. Smoking is a potent stimulus for the induction of endothelial dysfunction. Smoking is known to induce changes in the lipid profile, including lower HDL and increased oxidation of LDL, the latter of which is presumed to be associated with exposure of LDL to free radicals present in cigarette smoke.

Obesity and Physical Inactivity

Obesity, in the absence of other risk factors for atherosclerosis, may be associated with only a small increased risk of coronary artery disease. However, it is clearly associated with the development of dyslipidemia, hypertension and diabetes. Physical activity positively alters the lipid profile, blood pressure, and glucose tolerance, and improves cardiovascular and pulmonary functional capacity. Physical fitness, which can be more objectively quantified than physical activity, independently reduces the risk of coronary heart disease.

Genetic Factors (Family History)

Single gene mutations that alter lipid metabolism and thus are associated with accelerated atherogenesis have been identified. However, no other single gene mutations enhance the currently known atherogenic risk factors. Some patients with dyslipidemias, hypertension, diabetes mellitus and homocystinemia have complex polygenic disorders. Currently identifiable genetic abnormalities, however, account for only a small number of patients with premature coronary artery disease.

Miscellaneous

Many other markers for risk of acute coronary events have emerged, and research continues into the role they play in the pathogenesis of atherosclerosis and its complications (Fig. 9). When considered together, they can provide important information regarding risk stratification of patients (160, 161).

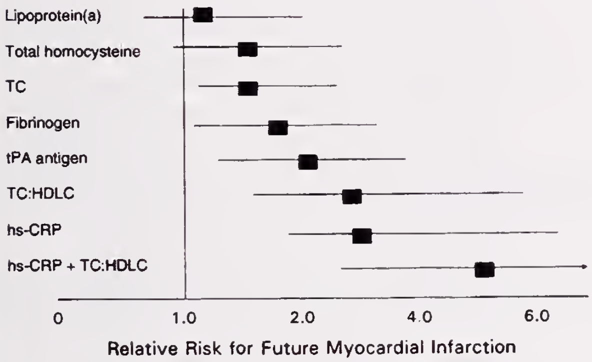

Fig. 9. Cardiovascular risk factor and relative risk for recurrent myocardial infarction among healthy middle-aged men. **TC.** - total cholesterol; **tPA.** - tissue plasminogen activator; **TC:HDLC.** - ratio of total to HDL-cholesterol; **hs-CRP.** - high-sensitivity C-reactive protein. (taken from ref. #160 and 161).

Conclusions

Many recent advances in our understanding of the molecular biology of atherogenesis and the mechanisms involved in the acute coronary syndromes have provided insights into potential future therapies. Risk factor modification is the cornerstone of prevention and should be pursued aggressively. However, we may in the future be actively treating at-risk patients with therapies that act at a cellular or molecular level (such as inhibitors of specific macrophage functions or direct MMP inhibitors) to impede atherosclerosis, rather than just modifying risk factors.

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Grand Rounds

Hemorheology in the Erythrocytoses

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Abstract

In vitro, rheological studies establish that whole blood viscosity and yield stress are high in patients with an erythrocytosis. However, a number of factors ensure that these patients, under physiological conditions, do not show the clinical features observed in other hyperviscosity states. These include red cell axial migration in flowing blood and "plug flow" in the largest vessels. In addition, a small increase in vessel diameter leads to large increases in blood flow, and generally high blood flows produce the lowest blood viscosity values. The increased hemoglobin levels and the increase in oxygen-carrying capacity at high hematocrit values compensate for the tissue hypoxia. In the "non-hypoxemic" erythrocytoses (polycythemia vera, idiopathic and apparent erythrocytosis), there is an increased incidence of vascular occlusion in untreated patients. The reasons for this include reduced peripheral blood flow, increased platelet-vessel wall interactions, and the demonstrated *in vitro* hyperviscosity which comes into play with abnormally low flow, seen *in vivo* under pathological conditions. In the erythrocytosis of hypoxemic lung disease and its associated hypoxemia, pulmonary vasoconstriction enhances susceptibility to hyperviscosity effects in particular. Moreover, the vasoconstriction caused by the hypoxemia prevents the normal adaptive changes of increased vessel diameter. Microcytic hypochromic red cell changes of iron deficiency do not cause a higher viscosity value at any given hematocrit value compared with normal red cells. However, in hypoxemic states oxygen-carrying capacity should be maximized, since the hemoglobin value is disproportionately lower at any given hematocrit in the presence of microcytic hypochromic cells compared with normal red cells.

Key Words: Hemorheology, blood viscosity, erythrocytosis, polycythemia vera, thrombosis, hypoxemia.

Introduction

Hemorheology is the study of blood flow and the deformation of blood cells and blood vessels. The erythrocytoses are a heterogenous group of disorders characterized by an increased proportion of red cells in the peripheral blood. The term "erythrocytosis" is preferred to "polycythemia," since "erythrocytosis" accurately describes the increase in red cell content of the blood, while "polycythemia" only means an increased number of cells in the blood, without specifying the cell type involved. There are various types of erythrocytosis, and a classification of them has recently been published (1). This is shown in the Table. Traditionally, the

Table
The Classification of the Erythrocytoses

Raised Hematocrit (females >0.48; males >0.51)

↓

RCM (interpreted against ICSH reference values)

Increased RCM
Absolute erythrocytosis
Primary erythrocytosis
Congenital Truncation of the Epo receptor
Acquired Polycythemia vera

Secondary erythrocytosis
Congenital, e.g., high oxygen affinity Hb, autonomous high Epo production
Acquired, e.g., hypoxemia, renal disease

Idiopathic erythrocytosis

Normal RCM
Apparent erythrocytosis

ICSH = Radionuclide panel of the International Council for Standardization in Haematology (104)
HCT = packed cell volume or hematocrit
RCM = red cell mass
Epo = erythropoietin

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erythrocytoses have been regarded as one of the conditions in which hyperviscosity of the blood occurs. This paper examines this statement by presenting the hemorheological studies that have been performed in the erythrocytoses, both *in vitro* and *in vivo*. *In vivo* results in selected forms of erythrocytosis are presented to show that they vary considerably, despite the similar *in vitro* results, which will be examined first.

In Vitro Hemorheology in the Erythrocytoses

The viscosity of a fluid is its resistance to flow. In steady streamline, so-called laminar, flow of a simple liquid in a straight, rigid tube, theoretically concentric cylindrical layers of fluid undergo shearing, i.e., they slide over each other. The force applied to a fluid layer is termed the "shear stress" (as measured in millipascals – mPa) and the velocity gradient obtained between adjacent layers of the fluid is the "shear rate" (inverse seconds – s^{-1}). Resistance to flow arises from friction between adjacent fluid layers; this frictional flow resistance is the fluid's viscosity (millipascal seconds – mPa•s) (2). Viscosity is given by the shear stress divided by the shear rate. Simply, if a trivial force on a fluid layer produces a high velocity of that layer relative to an adjacent layer, then the viscosity of the fluid is very low and vice versa.

Simple fluids that show the same viscosity value irrespective of the shear rate at which they are measured are termed "Newtonian fluids." Whole blood, unlike plasma, behaves in a non-Newtonian fashion. That is, its viscosity is markedly dependent on the prevailing shear rate. At high shear rates, above approximately 100 s^{-1} (3), whole blood achieves its minimum viscosity value. In this situation, the red cells maximally deform and align themselves to produce the minimum resistance to flow. With progressive lowering of the shear rate below this level, red cell aggregation occurs increasingly and the viscosity rises exponentially. Thus, in measuring blood viscosity, it is important to fix the shear rate at which the value is being determined. If blood is stationary, a force, termed the "yield stress value," is required to initiate flow.

The single most important determinant of whole blood viscosity is the red cell content of the blood, reflected by the hematocrit. In the earliest experiments using capillary viscometers, it was observed that blood viscosity did not increase significantly until the hematocrit was above 0.55 (4). However, with the use of rotational viscometers, where the shear rate can be fixed, it can be shown that there is a linear relationship between the logarithm of blood viscosity and hematocrit at each shear rate. In addition, the relationship between blood viscosity and hematocrit becomes steeper as the shear rate is reduced (Fig. 1). Thus, in the physiological range of hematocrit from 0.40–0.50, there is a 25% rise in viscosity at a shear rate of 230 s^{-1}, but a nearly 80% rise at a shear rate of 0.77 s^{-1}.

The yield stress value reflects the attractive forces between red cells in stationary conditions (5). The value for yield stress depends on the plasma protein concentration, notably globulin and fibrinogen (6, 7) at any given hematocrit, but the hematocrit is the dominant influence on the yield stress value. There are different methods of measuring yield stress. Thus, there is no precise agreement on the hematocrit effect, but best-fit relationships between the two parameters have been given by the logarithm of yield stress against hematocrit (8) or the cubed root of yield stress against hematocrit. Using a different measuring system, a tenfold rise in yield stress has been shown to occur between a hematocrit of 0.45 and 0.55 (9).

From these observations of viscosity and yield stress, there can be no doubt that the raised hematocrit values observed in the ery-

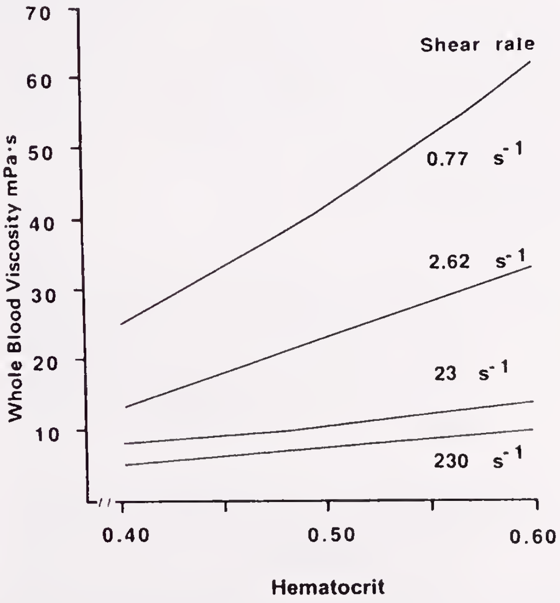

Fig. 1. The relationship of whole blood viscosity [millipascal seconds- mPa•s] measured *in vitro* to hematocrit at a range of shear rates [inverse seconds-s^{-1}]. Reproduced with permission (8).

throcytoses cause a hyperviscosity state as measured *in vitro*.

Relationship of *In-Vitro* Observations and *In-Vivo* Findings under Physiological Conditions

The volume rate of fluid (Q) flowing in a steady, streamline fashion in a rigid, straight tube depends on the pressure gradient (P) along the tube, the length (l) and radius (r) of the tube and the viscosity (η) of the fluid according to the Hagen-Poiseuille equation:

$$Q = \frac{\Delta P \, \pi \, r^4}{8 \, l \eta}$$

Q = flow; ΔP = mean arterial pressure – venous pressure; r = radius of vessel; l = length of vessel; η = viscosity

This formula was determined in the middle of the last century. However, it gives a first approximation for blood flow through an organ (2):

$$Q = \frac{\Delta P}{\text{Vascular resistance} \times \text{viscosity}}$$

The flow resistance is partly derived from the geometrical resistance of the conducting blood vessels (vascular resistance) and partly the flow resistance of blood (blood viscosity).

In vivo measurements of apparent blood viscosity under physiological conditions are much lower than those obtained *in vitro* (10–12). The conditions under which blood viscosity is measured *in vitro* oversimplify the complex conditions existing *in vivo* (13). The major factors involved *in vivo*, which lead to the complexity, are as follows (8):

1. In the arteries, down to a diameter of approximately 100 μm, flow is determined by inertial rather than viscous forces. The inertial force is given by the product of the mean flow velocity and the vessel diameter.

2. Flow in vessels leads to axial migration of red cells, giving a relatively cell-free layer of plasma, which has low viscosity, around the central core of red cells. In large vessels, this phenomenon can lead to a non-sheared central core of cells — "plug flow" (13). In vessels below 300 μm in diameter, axial migration leads to a significantly wide plasmatic zone compared with the dimensions of the vessel and the cellular components (14).

3. In the microcirculation the hematocrit is lower than in larger vessels, and in capillaries the flow must be considered to be determined by plasma viscosity and the deformability of individual cells.

4. Vessel diameter can profoundly affect flow, and this is seen particularly in the arterioles. Examination of the Hagen-Poiseuille formula shows that while flow is inversely related to viscosity, it is directly related to the fourth power of the radius. Thus, a 10% increase in vessel diameter leads to an approximately 50% increase in blood flow.

5. The shear rates encountered in the circulation are sufficiently high to ensure minimum blood viscosity values.

In addition, since one of the main objectives of blood flow is to maintain oxygen delivery to the tissues, the high hemoglobin value in the erythrocytoses, and hence the high oxygen-carrying capacity of the blood, mitigates the influence of the increased blood viscosity in reducing blood flow and, thus, reducing oxygen delivery to the tissue. This situation is quite dissimilar to all other forms of hyperviscosity, where patients are generally anemic. Finally, when considering blood flow *in vivo*, one has to appreciate that it is highly dynamic and that disturbances of the normal cardiovascular physiology, such as heart failure and vessel disease, can lead to significant deviations from the normal physiology.

Clinical Observations in "Non-hypoxemic" Erythrocytoses

Included in this group of disorders are polycythemia vera, idiopathic and apparent erythrocytosis, and secondary renal erythrocytosis. In all of these forms of erythrocytosis, an increased incidence of vascular occlusive events has been found.

In polycythemia vera (PV), which characteristically presents at approximately 60 years of age, vascular complications occur in 30–50% of patients at presentation (15). The occlusive complications occur equally in arteries and in veins. A similar observation has been made in the treatment phase of PV (16). If patients remain untreated following presentation, the median survival is 18 months, with the majority dying of vascular occlusion (17). The arterial complications in PV are of two types — larger vessel and microvascular. The larger vessel arterial occlusion may occur in any part of the circulation, but it does appear that the cerebral vessels are particularly prone to thrombosis (15, 17, 18). Microvascular occlusions are a particular feature of PV not seen in other forms of erythrocytosis. They are almost certainly due to quantitative and qualitative platelet changes, since similar complications occur in the related myeloproliferative disorder, primary thrombocythemia (19–21). The typical features are erythromelalgia and/or purplish pregangrenous changes of the digits, usually, but not always involving the lower limbs. In the cerebral circulation, transient episodes of neurological dysfunction, for example, amaurosis fugax, hemiparesis and epileptic attacks, may occur (22–24).

In idiopathic erythrocytosis, there is an age presentation similar to that of PV, but with a marked male predominance (25). In one study of these patients, half presented with arterial complications, notably intermittent claudication, and 17% with superficial or deep vein thrombosis (26). In another study, thrombo-embolic events were similar to those observed in PV (27). Examination of the cause of death showed that, as in PV, a cerebral occlusive event was particularly likely to be responsible (26, 27).

With regard to apparent erythrocytosis, two retrospective studies have been published. Burge et al. (28) reported that in a group of patients followed for a median of 4 years, the mortality was six times greater than expected for a sex- and age-matched population. Four of the observed six deaths were due to vascular occlusion. Weinreb and Shih (29) described a larger cohort of patients followed for 12 years. In patients with, dominantly, a reduced plasma volume, 35% had had a major vascular occlusive event within 5 years of presentation.

In secondary non-hypoxemic erythrocytoses, vascular occlusion has been anecdotally reported. For example, patients with post-renal-transplant erythrocytosis often develop thrombotic complications (30), the incidence of which is much greater than in those post-transplant patients who do not develop an erythrocytosis (31). A thrombotic complication may lead to the discovery of a cause of an erythrocytosis, such as hypernephroma (32) and fibroids (33).

The role of the hematocrit level in determining the incidence of vascular occlusion events in PV has been thoroughly explored. There is general agreement that the more adequately the hematocrit is lowered, the less likely are these complications (16, 34, 35), and that, ideally, the hematocrit should be controlled at less than 0.45. In idiopathic erythrocytosis, similar observations have been made, indicating a positive correlation between the hematocrit and vascular occlusion (36, 37).

Evidence of Hyperviscosity Syndrome and Blood Flow in the "Non-hypoxemic" Erythrocytoses

From the presentation of the clinical findings in these forms of erythrocytosis, it can be concluded that a study of cerebral blood flow (CBF) would have relevance. Cerebral blood flow rates have been extensively measured both at presentation and following treatment to lower the hematocrit to normal. For each patient and in each group of erythrocytosis, a negative correlation exists between CBF and hematocrit (38–40). The typical findings are shown in Fig. 2. From the results of *in vitro* blood rheology in the erythrocytoses presented earlier, it

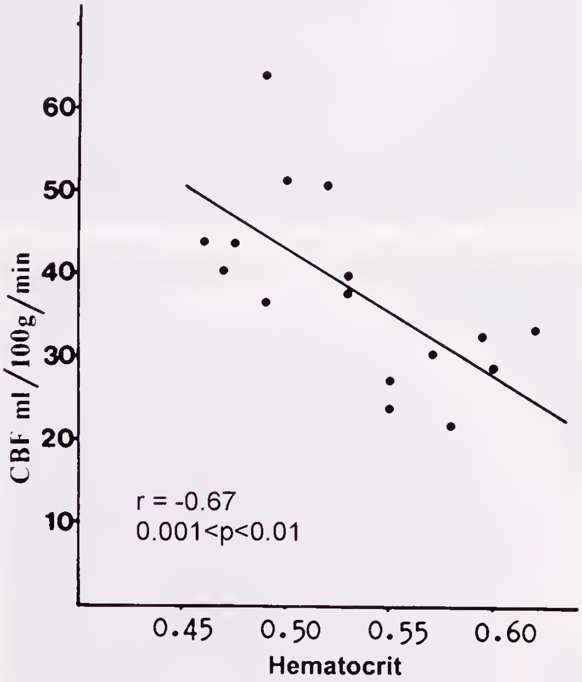

Fig. 2. The inverse relationship between cerebral blood flow (CBF) and hematocrit in patients with polycythemia vera and idiopathic erythrocytosis (some patients had been phlebotomized to achieve a lower hematocrit). Reproduced with permission (8).

could be argued that the observed hyperviscosity at raised hematocrit values limits CBF. However, a number of observations negate that conclusion. First, if hyperviscosity of the blood was a limiting factor, one would expect that vessel dilatation would occur to improve flow. Yet comparison of the retinal appearances in the hyperviscosity of macroglobulinemia and of PV shows completely dissimilar findings (Fig. 3). While in macroglobulinemia the vessels are grossly distended, any changes are minimal in PV. Second, the reactivity of the cerebral vessels to hypercapnia, which causes vessel dilatation, is not impaired at presentation compared with the results obtained following lowering the hematocrit to normal (41). Thus, it must be concluded that the observed changes in CBF at elevated hematocrit values are a result of the concomitant rise in hemoglobin value and in oxygen-carrying capacity. Studies of patients with elevated plasma viscosity and hyperleukocytosis confirm this view (42, 43).

Limb blood flow has also been studied in these patients. As is found in the cerebral circulation, there is an inverse relationship between limb blood flow and hematocrit (44). Again, it is the maintenance of oxygen transport to the limbs that is the relevant controlling influence. Animal experiments have also led to the conclusion that the raised blood viscosity in an erythrocytotic state does not limit flow (11, 45). There is a further factor to be considered

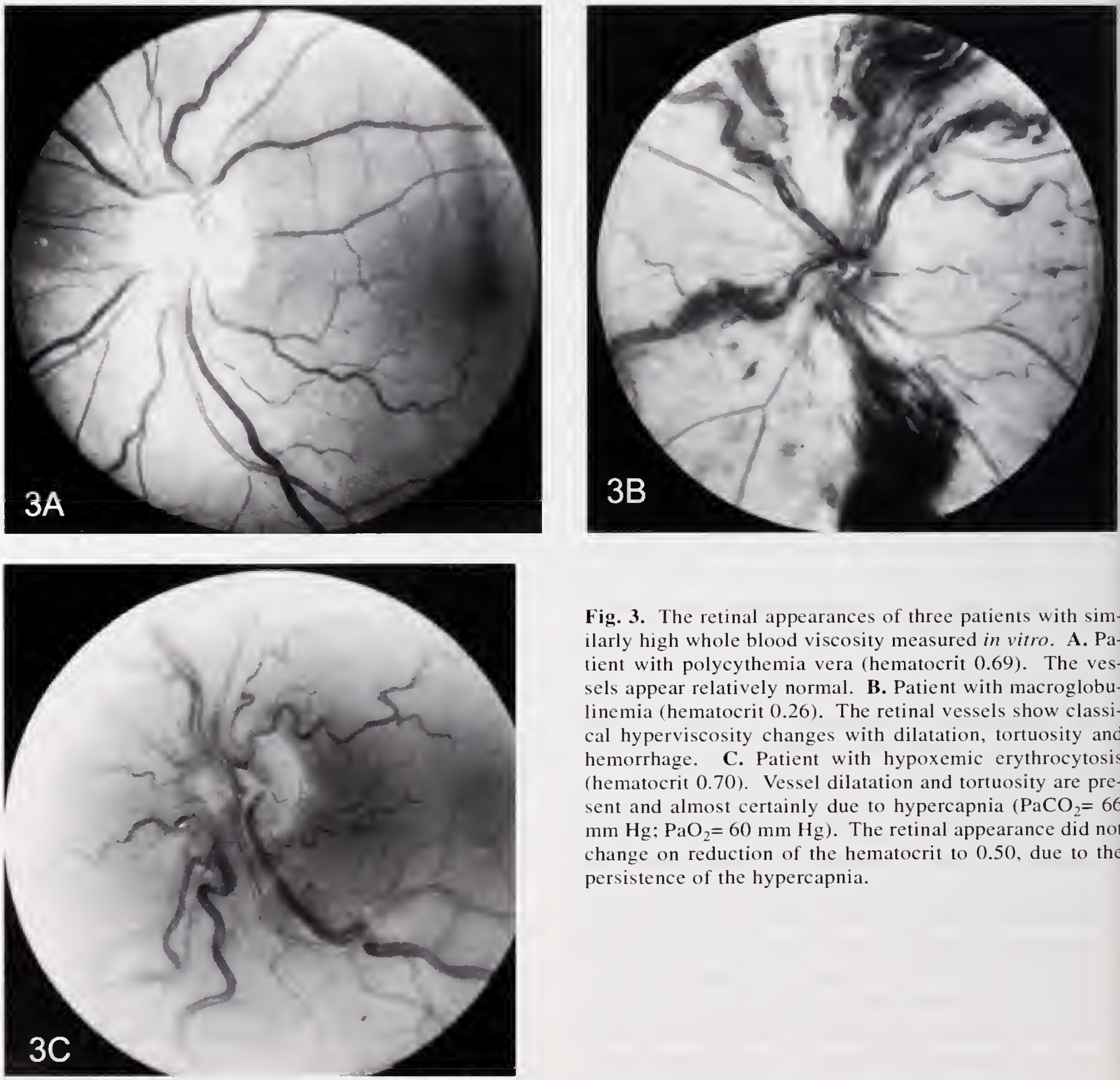

Fig. 3. The retinal appearances of three patients with similarly high whole blood viscosity measured *in vitro*. **A.** Patient with polycythemia vera (hematocrit 0.69). The vessels appear relatively normal. **B.** Patient with macroglobulinemia (hematocrit 0.26). The retinal vessels show classical hyperviscosity changes with dilatation, tortuosity and hemorrhage. **C.** Patient with hypoxemic erythrocytosis (hematocrit 0.70). Vessel dilatation and tortuosity are present and almost certainly due to hypercapnia ($PaCO_2$= 66 mm Hg; PaO_2= 60 mm Hg). The retinal appearance did not change on reduction of the hematocrit to 0.50, due to the persistence of the hypercapnia.

in muscle flow, and that is the effect of muscle contraction. Using an isolated dog calf muscle with dilated vessels, rhythmic muscle contraction has been shown to offset the effects of the raised blood viscosity when the hematocrit is raised (46). Possibly, muscle contraction leads to the emptying of small veins, leading to a reduction in post-capillary pressure, and also facilitating the passage of red cells through the pre-capillary and capillary networks.

Relationship of Clinical Findings in the Non-hypoxemic Erythrocytoses and Hemorheology

While the reduction in peripheral blood flow might not be caused by hyperviscosity per se, the change might increase the likelihood of thrombosis. Certainly, it is established that slow or static flow in veins enhances the risk of thrombus formation (47) and venous thrombosis is more common in the elderly and the obese (48). In the arterial circulation, if the cerebral blood flow findings are typical, then an approximate 30% reduction in flow occurs between hematocrit values of 0.45 and 0.55 (Fig. 1), and this could enhance the thrombotic tendency.

There are two other relevant considerations: platelet-vessel wall interactions, and the role of hemorheological blood changes once abnormally low flow conditions prevail. Increased red cell concentration enhances platelet contact with the vessel wall. In flowing blood, there is an axial migration of the red cells, with a displacement of the platelets (and white cells) toward the vessel wall, into the so-called plasmatic zone, which gets narrower as the hematocrit rises (49). In this context, it is important to remember that platelet counts are presented as a number per unit volume of whole blood, although in fact the platelets are only distributed in the plasma. In effect, in terms of the physiological function of platelets, it is the plasma platelet count that should be considered. Thus, as the prevailing hematocrit rises, the platelet concentration in the plasma rises, and in flowing blood, the platelets are brought into closer contact with the endothelium. While platelets do not adhere to the intact endothelium, *in vitro* systems examining the adhesion of platelets to the subendothelium demonstrate greater adhesion at increased hematocrit values (50–52). In addition, nitric oxide produced by the endothelium acts as a platelet anti-aggregant, but is removed by combination with hemoglobin. Higher hemoglobin levels lead to a more effective neutralization of nitric oxide (53).

Thrombus formation preferentially occurs around bifurcations, beyond stenoses and at atheromatous plaques, where flow is often disturbed. The shearing forces modify platelet binding sites, leading to von Willebrand factor (vWF) binding to platelet Gp Ib and Gp IIb/IIIa (54–56). Vortices, with reverse flow, can be formed (57). At the edges of the vortices, the activated platelets can adhere via vWF to exposed subendothelial components of the vessel wall. From the previous discussion, it is not surprising that this occurs more readily at high platelet counts and hematocrit values. Platelet aggregation and adhesion, and thrombus formation are initiated by the release of adenosine diphosphate (ADP) from damaged vessel-wall cells, platelets and red cells (58, 59). In veins, thrombi characteristically start in the pockets of venous valves. Blood flow in veins accelerates as it passes through the valves, but then vortices and stagnation occur in the downstream pockets (57). In these sites, platelet aggregation followed by fibrin formation occurs with a greater admixture of red cells than in arteries, due to the slower blood flow characteristics (60). In PV, apart from an increase in platelet concentration, there are intrinsic platelet abnormalities favoring the initiation or stabilization of a thrombus. These include a loss of PGD_2 receptors (61) and increased anti-plasmin levels (62).

The microvascular occlusive events of PV are due to either platelet embolization from proximal atheromatous plaques (15, 63) or local aggregation and adhesion, typically to arteriolar walls, where thrombi can form and occlude the vessel (64–66). Increased platelet formation of thromboxane in asymptomatic PV has been demonstrated, presumably reflecting spontaneous activation *in vivo* (67). This activation has been shown to precede arterial microvascular thrombosis (68, 69).

With respect to hemorheological factors following reduction or cessation of flow, when tissue hypoxia occurs due to a fall in perfusion pressure, reactive vasodilation occurs. As presented earlier, the small changes in vessel diameter can dramatically improve flow. Generally, in the non-hypoxemic erythrocytoses these compensatory changes are not impaired. However, there may be some reduction in reactivity if there is vessel disease (70, 71) in the vicinity of ischemic tissue (72). Once maximal vasodilation has occurred, blood flow is then dependent on the perfusion pressure and the rheological properties of the blood (73). It is in this situation that the demonstrated hyperviscosity of the blood in the erythrocytoses *in vitro* comes into play. As the blood flow falls, the viscosity increases and a vicious circle is initiated. If stasis occurs, the high yield stress of blood, which is present at high hematocrit values, may be a critical determinant of the outcome (74). Given these considerations, it is not surprising that animal experiments have shown that the area of non-perfused brain following vessel occlusion is greater in hypertransfused animals than in those animals with normal hematocrit values (75, 76). There is similar evidence in humans. For example, the size of cerebral infarct following carotid occlusion (77) and the area of retinal non-perfusion following retinal vein occlusion (78) are directly correlated with the hematocrit value.

The Hypoxemic Secondary Erythrocytoses

While the *in vitro* rheological findings are the same in these forms of erythrocytosis as in the non-hypoxemic types, there are different circulatory conditions prevailing *in vivo*. To illustrate this, two hypoxemic secondary erythrocytoses will be considered: chronic lung disease and high-oxygen-affinity mutant hemoglobins.

When hypoxemia is due to chronic lung disease, there is an inverse relationship between the arterial oxygen saturation (SaO_2) and the red cell mass, hemoglobin and hematocrit values. However, a number of additional factors play a part in an individual patient. These include the presence of carbon monoxide in smokers, the extent of hypercapnia, differences in renal blood flow, acid-base status, changes in extracellular pH, variability in the SaO_2 position of the oxygen dissociation curve, the capacity of the marrow erythropoietic response, and changes in plasma volume (79).

The development of an erythrocytosis in patients with chronic lung disease is associated with an increased risk of cor pulmonale (80) and a median survival in the order of 2–3 years (81). Death is usually ascribed, not unexpectedly, to a cardiopulmonary cause (82). Vascular occlusive events, such as cerebral infarction, deep vein thrombosis and pulmonary embolus do occur, but are less frequently described and less precisely defined than in PV, probably due to a shorter survival of these patients and the complex interactions of numerous other factors in their medical symptoms/signs.

The question that commonly arises in the management of these patients is the balance between the effect of the increased hemoglobin level in improving oxygen transport and the effect of increased hematocrit value on blood viscosity. Hypoxemia and hypercapnia lead to peripheral vessel dilation and pulmonary vessel vasoconstriction. The effects on the peripheral vessels can readily be shown by the retinal appearances (Fig. 3). Measurements of CBF in these patients present rather variable results, with some patients showing a reduction in CBF while others show a considerable increase, despite the hyperviscosity state, due to cerebral vessel dilation, in turn due to hypercapnia (83, 84). Generally, cerebral oxygen transport is maintained or increased (83).

It is in the pulmonary vasculature of these patients that there are specific hemorheological problems. The chronic hypoxemia, which causes pulmonary vasoconstriction, leads to smooth muscle hyperplasia and less compensatory vasodilation to mitigate the hyperviscosity of the blood. Thus, both the change in pulmonary vessel geometry and the increased blood viscosity lead to a high pulmonary vascular resistance (85, 86). Reduction of the hematocrit by phlebotomy, which also causes a reduction in blood volume in some patients, has been shown to reduce pulmonary vascular resistance (79, 87, 88). The balance between blood oxygen-carrying capacity and viscosity has been addressed by the study of Weisse et al. (88), who showed that reducing the hematocrit to 0.50–0.52 led to an improvement in exercise tolerance. Exercise tolerance was not enhanced when hematocrit was reduced further to 0.45. Fortunately, current medical care in these patients includes the use of chronic oxygen therapy. This has the dual benefit of lowering the hematocrit and pulmonary vascular resistance, and leads to an improvement in morbidity and prognosis (81).

Occasionally, patients with hypoxemia, particularly those that have been phlebotomized, have iron-deficient red cell changes with low mean corpuscular volume (MCV) and low mean corpuscular hemoglobin (MCH) values. There is extensive literature examining the effect of these red cell changes on blood viscosity. The overall opinion is that, at a given hematocrit, microcytic hypochromic red cells do not produce a higher viscosity value than do normochromic normocytic cells (89–93). However, it is essential to realize that some blood analyzers underestimate the true hematocrit in the presence of microcytic hypochromic red cells (94), a fact not appreciated by some authors. This has led them to incorrectly interpret the effect of microcytic hypochromic red blood cells on blood viscosity (95, 96).

On the other hand, in hypoxemia, oxygen-carrying capacity should be maximized. In the presence of these microcytic hypochromic red cells, the hematocrit and hence viscosity of the blood is greater than for blood containing normochromic normocytic cells at the same hemoglobin value (97). Thus, judicious iron therapy may be indicated in some hypoxemic patients to correct the microcytic hypochromic changes. Unfortunately, this will increase the frequency of phlebotomy to achieve a lower hematocrit value.

With respect to high-oxygen-affinity hemoglobins and resultant tissue hypoxemia, more than 40 different mutant hemoglobins with increased oxygen affinity, nearly all chain variants, have been described. The *in vivo* adaptations to the reduced oxygen delivery to the tissues include increased hemoglobin levels and cardiac output. Markedly increased cerebral blood flow, despite elevated hematocrit values, has been demonstrated in members of one family with Hb Yakima (98). Some patients with particularly high hematocrit values do develop nonspecific "hyperviscosity" symptoms of headache and confusion. Originally, it was felt that the maintenance of high peripheral blood flows reduced the incidence of vascular occlusive events compared with patients with non-hypoxemic erythrocytoses. However, individual cases of deep vein thrombosis and myocardial ischemia or infarction have been described (99-101). Now that larger numbers of patients with high-oxygen-affinity hemoglobins have been followed, the impression is that, with the development of age-related vessel and cardiac disease, these patients are prone to occlusive events, particularly in the cerebral circulation (VF Fairbanks, 1999, personal communication). Since phlebotomy obviously does not correct the basic defect, exchange transfusion with normal blood has been used in these patients with cardiac ischemia (102). The particular benefit of high-oxygen-affinity hemoglobin occurs at high altitudes, where oxygen uptake in pulmonary alveoli is facilitated by a left-shifted oxygen dissociation curve, a feature commonly found in animal species adapted to a life at high altitude (103).

Summary

The different forms of erythrocytosis provide an intriguing comparison in terms of *in vivo* hemorheological changes. Under physiological conditions, the hyperviscosity state demonstrated *in vitro* in the erythrocytoses does not present a rheological problem, although platelet-vessel wall interactions are enhanced. However, if circulatory adaptations in the various types of erythrocytoses are limited or exhausted or other general circulatory disturbances occur, the blood hyperviscosity plays a critical role in reducing flow and causing greater ischemia and tissue damage.

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Radiation Therapy to Inhibit Restenosis:

Early Clinical Results

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Abstract

Background: Although several early trials indicate that treatment of restenosis with radiation therapy is safe and effective, the long-term impact of this new technology has been questioned. The objective of this report is to document angiographic and clinical outcome 3 years after treatment of restenosis of stented coronary arteries with catheter-based iridium-192 (^{192}Ir).
Methods: A double-blind, randomized trial compared ^{192}Ir with placebo sources in patients with previous restenosis after coronary angioplasty. Over a 9-month period, 55 patients were enrolled; 26 were randomized to ^{192}Ir and 29 to placebo.
Results: At 3-year follow-up, target-lesion revascularization was significantly lower in the ^{192}Ir group (15.4% vs. 48.3%; $p < 0.01$). The dichotomous restenosis rate at 3-year follow-up was also significantly lower in ^{192}Ir patients (33% vs. 64%; $p < 0.05$). In a subgroup of patients with 3-year angiographic follow-up not subjected to target-lesion revascularization by the 6-month angiogram, the mean minimal luminal diameter between 6 months and 3 years decreased from 2.49 ± 0.81 mm to 2.12 ± 0.73 mm in ^{192}Ir patients, but was unchanged in placebo patients.
Conclusions: The early clinical benefits observed after treatment of coronary restenosis with ^{192}Ir appear durable at late follow-up. Angiographic restenosis continues to be significantly reduced in ^{192}Ir-treated patients, but a small amount of late loss was observed between the 6- month and 3-year follow-up time points. No events occurred in the ^{192}Ir group to suggest major untoward effects of vascular radiotherapy. At 3-year follow-up, vascular radiotherapy continues to be a promising new treatment for restenosis.

Key Words: Coronary artery angioplasty, restenosis, radiation therapy, clinical trials.

The need for repeat procedures due to restenosis continues to be the Achilles heel of coronary angioplasty. Restenosis can be divided into two general concepts. The first, recoil and remodeling, refers to the mechanical collapse and constriction of the treated vessel. The second, intimal hyperplasia, refers to the proliferative response to injury, and consists largely of smooth muscle cells and matrix formation (1, 2). Coronary stents provide a luminal scaffolding that virtually eliminates classic recoil and remodeling; they have been shown to reduce restenosis by approximately 30% (3, 4). Stents, however, do not decrease but, in fact, increase the proliferative component of restenosis. Other benign fibroproliferative disorders such as keloid formation and heterotopic ossification have been successfully treated with radiation therapy. In several animal models of restenosis, local, catheter-based ionizing radiation or radioactive stents have demonstrated significantly reduced neointimal proliferation (5–8). These reports have encouraged the initiation of several clinical trials. We designed the Scripps Coronary Radiation to Inhibit Proliferation Post-Stenting (SCRIPPS) trial as a double-blind, placebo-controlled, randomized trial to test this new treatment modality in restenotic stented human coronary arteries.

Methods

In the SCRIPPS trial, patients with previous restenosis and stent implantation were randomized to receive a 0.03-inch ribbon containing either iridium-192 (^{192}Ir)-sealed sources at its tip (Best Industries, Springfield, VA) or a placebo ribbon with inactive sources. Iridium-192 dosimetry was calculated using intravascular

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ultrasound (IVUS) measurements. The radiation oncologist and physicist used information from the IVUS image to determine a dwell time that provided 800 cGy to the internal elastic membrane furthest from the radiation source, provided that no more than 3,000 cGy was delivered to the internal elastic membrane closest to the radiation source. All angiographic and IVUS measurements were performed at an independent core ultrasound laboratory by investigators blinded to procedural information and patient assignment. Measurements that were captured included minimum luminal diameter, acute gain, late lumen loss, late lumen loss index and restenosis (≥ 50% diameter stenosis at follow-up).

Results

Between 3/24/95 and 12/22/95, 55 patients were randomized; 26 were assigned to ^{192}Ir and 29 to placebo. Baseline clinical and angiographic characteristics were similar for both groups. Many study patients had one or more baseline characteristics associated with increased restenosis risk, including diabetes, unstable angina, more than one previous restenosis, ostial lesion location, vein graft target, and lesion length ≥ 10 mm.

At the 30-day endpoint, the initial procedure was successful in 96.2% of ^{192}Ir and 96.6% of placebo patients (p = ns). Six-month angiographic follow-up was obtained in all patients except one in the ^{192}Ir group who sustained stent thrombosis and one in the placebo group who refused follow-up and died at 8 months due to cardiac arrest. One additional patient in the ^{192}Ir group who had late angiographic follow-up (without evidence of restenosis) was disqualified from angiographic analysis for technical reasons.

Angiographic indices of restenosis were markedly different in treated vs. placebo patients (Fig. 1). Late luminal loss was significantly lower in the ^{192}Ir group (0.38 ± 1.06 mm vs. 1.03 ± 0.97 mm; p = 0.009). Notably, the late lumen loss index (9), a sensitive measure of a therapy's ability to preserve the post-procedural luminal diameter, was significantly lower in the ^{192}Ir group (0.12 ± 0.63 vs. 0.60 ± 0.43; p = 0.002). Using a dichotomous definition, angiographic restenosis (≥ 50% diameter stenosis at follow-up) either within the stent or at the stent border (outside the stent but still covered by the study ribbon) was only 16.7% in the ^{192}Ir group compared to 53.6% for placebo patients (p = 0.025) (Fig. 2). Restenosis limited to the stented segment occurred in only 8.3% of the ^{192}Ir group compared to 35.7% of placebo patients (p = 0.024).

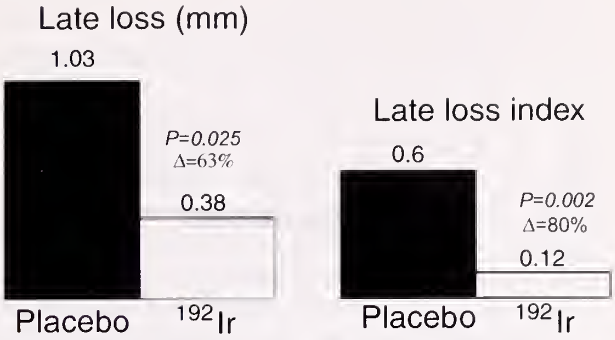
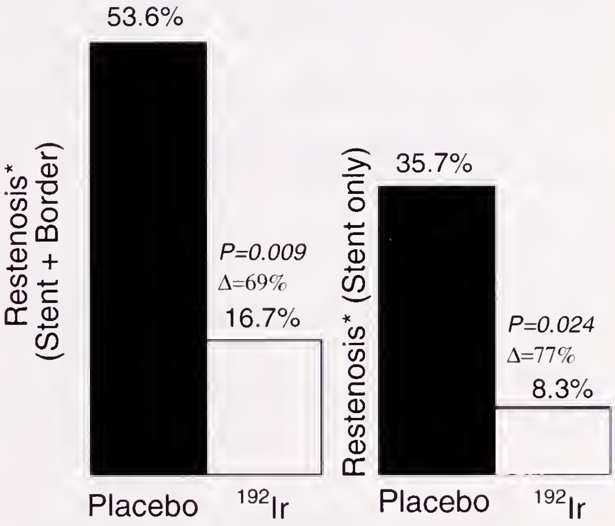


Fig. 1. Comparison of late luminal loss and late loss index in placebo versus ^{192}Ir patients. Late loss was reduced by 63% while late loss index was reduced by 80%.

The angiographic results were supported by independent intravascular ultrasound analysis (Fig. 3). By intravascular ultrasound analysis, there was no significant change in stent area or stent volume (Fig. 3A) between the immediate post-procedure and follow-up periods. The decrease in mean lumen area at follow-up was smaller in the ^{192}Ir group (0.7 ± 1.0 mm^2 vs. 2.2 ± 1.8 mm^2; p = 0.003), as was the increase in area of tissue growth (Fig. 3B) within the stent struts (0.7 ± 0.9 mm^2 vs. 2.2 ± 1.8 mm^2; p = 0.003). The decrease in lumen volume was



*(≥ 50% diameter stenosis)

Fig. 2. Comparison of a dichotomous definition of angiographic restenosis (≥ 50% diameter stenosis) between placebo and ^{192}Ir patients. Restenosis was reduced by 69% when both the stent and stent border were included in the analysis. Restenosis was reduced by 77% when only the stented region was measured.

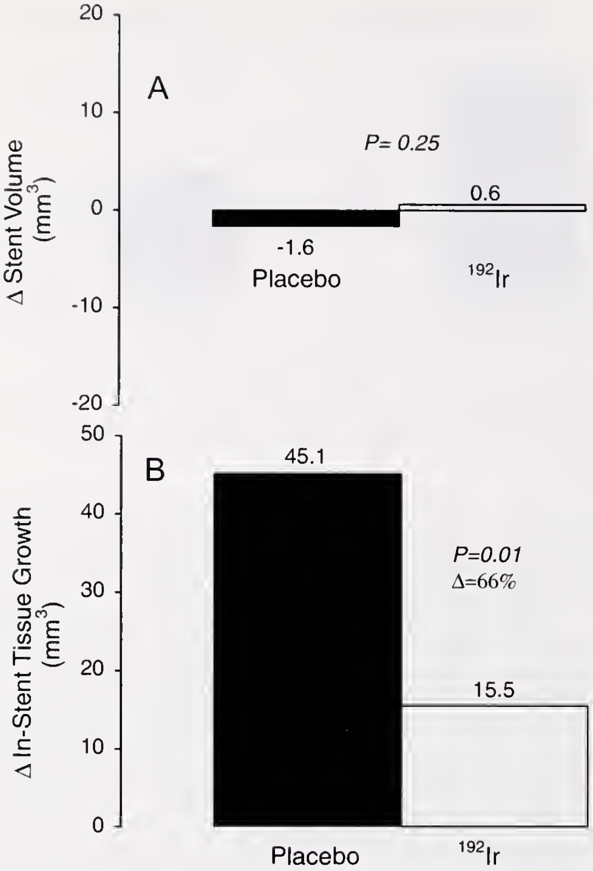


Fig. 3. Intravascular ultrasound measurement of change in mean stent volume and change in the volume of tissue growth over a 6-month period in placebo versus ^{192}Ir patients. **A.** The stent volume did not change in either placebo or treated patients. **B.** Placebo patients demonstrated nearly three times the volume of tissue growth within stent struts at the follow-up examination.

also smaller in the ^{192}Ir group (16.4 ± 24.0 mm^3 vs. 44.3 ± 34.6 mm^3; $p = 0.008$), as was the increase in volume of tissue growth within stent struts (15.5 ± 22.7 mm^3 vs. 45.1 ± 39.4 mm^3; $p = 0.0091$).

Clinical follow-up was obtained for all patients at a mean time of 12.2 ± 2.9 months (12.0 ± 2.8 vs. 12.2 ± 3.1 months in ^{192}Ir and placebo groups, respectively; p = ns). The difference in angiographic restenosis rates was supported by a reduction in target lesion revascularization in the ^{192}Ir group (11.5% vs. 44.8%; $p = 0.008$) (Table). Composite clinical events (death, myocardial infarction, stent thrombosis, or target lesion revascularization) were also significantly less frequent in ^{192}Ir patients (15.4% vs. 48.3%; $p = 0.011$).

Discussion

The SCRIPPS trial is the first double-blind, placebo-controlled, randomized trial of radiotherapy in patients undergoing coronary angioplasty. Although our patient numbers were small, we observed a striking reduction in restenosis when patients were treated with ^{192}Ir gamma radiation. This reduction in restenosis was similar for angiographic, ultrasonographic and clinical endpoints. Thus, gamma radiation using ^{192}Ir is the very first therapeutic agent, of more than 50 clinically tested (10), to demonstrate an impact on neointima formation after angioplasty.

Other clinical trials of intravascular gamma radiation therapy to reduce restenosis are limited, but data are rapidly accumulating. In one very early study, Bottcher (11, 12) used ^{192}Ir to treat 13 patients with angioplasty plus stent implantation for femoral artery restenosis. All 13 patients also received 12 Gy radiation immediately after the procedure. Clinical follow-up indicated no recurrent restenosis during the sub-

TABLE
Clinical Events at 12-Month Follow-up

	^{192}Ir (n = 26)	Placebo (n = 29)	p
Death	0	1 (3.4%)	ns
MI*	1 (3.8%)	0	ns
Target lesion revascularization	3 (11.5%)	13 (44.8%)	0.008
Death, MI, stent thrombosis or target lesion revascularization	4 (15.4%)	14 (48.3%)	0.011
Death, MI, stent thrombosis, target lesion revascularization or non-target lesion revascularization	5 (19.2%)	18 (62.1%)	0.002

*MI = myocardial infarction

sequent 3–27 months. Steidle (13) also used ^{192}Ir to treat 24 patients for femoral artery stenosis with stent implantation. Percutaneous radiation therapy with 2.5 Gy per day for 5 days, for a total of 12.5 Gy, was administered to 11 of these 24 patients. Over a 7-month follow-up period, reocclusion occurred in 2 of the 11 patients in the radiation group and 5 of the 13 patients in the no-radiation group. Condado et al. (14) treated 21 patients undergoing coronary angioplasty with ^{192}Ir. While there was no control group, follow-up results were very encouraging, with a reported late loss index of 0.19 and restenosis rate of 27.3%.

Beta emitters differ from the gamma energy used in the above trials in that such radiation is less penetrating and more easily shielded, making it somewhat easier to handle in the catheterization laboratory environment. However, questions have been raised concerning the ability of a beta emitter to provide therapeutic radiation doses to the required depth. The results to date are conflicting (15). Verin et al. (16) treated 15 patients undergoing coronary angioplasty with ^{90}Y, a beta emitter. The results were disappointing, with a loss index of 50% and restenosis rate of 40% at 6 months. These investigators are currently pursuing subsequent trials using higher dose prescriptions. King et al. (17) used ^{90}Sr/Y, also a beta emitter, to treat 21 patients undergoing coronary angioplasty. Although there was no control group, the reported 6-month restenosis rate of 17% and loss index of 0.05% were very encouraging. These favorable results inspired a 1,400-patient, multicenter, randomized trial (the Beta-Cath™ trial) for *de novo* lesions and a 476-patient trial (the START trial) to test ^{90}Sr/Y in patients with in-stent restenosis. The recently reported 6-month angiographic and clinical results of the START trial were strongly positive, providing significant confirmation of radiation's efficacy in limiting restenosis. Compared to the placebo group, patients with in-stent restenosis receiving radiation sustained a 36% reduction in subsequent restenosis, from 45% to 29% ($p = 0.001$). Clinical results were also impressive, with the need for target vessel revascularization falling from 24% in the placebo group to 16% in treated patients ($p = 0.026$) (NoVoste Announces Results of START TRIAL, NoVoste Press Release, March 12, 2000.)

Finally, clinical investigations of very novel radiation delivery systems are just beginning. A beta-emitting (^{32}P) coronary stent has recently been tested in a small feasibility trial (18), as has a beta-emitting (^{188}Re) liquid-filled balloon catheter. The results of these trials are pending.

The excitement generated by these results must be tempered by several concerns. Most important are the unknown long-term effects of intracoronary radiation. While previous experience with radiation therapy for benign disorders suggests no significant increased risk at these doses, patients treated in these early clinical trials must continue to be followed carefully over a longer time period. Further follow-up must also be undertaken to assure that the reduction in restenosis reported above is durable and will not dissipate over time.

The work ahead necessary to develop and refine clinically useful vascular radiotherapy systems is daunting. There are many unanswered questions. What will be the most practical catheter-based gamma radiation system? Can beta radiation penetrate deep enough into the diseased vessel wall to provide clinical efficacy? Will radioactive stents be effective, or will they be limited by dose heterogeneity, edge effect, and/or thrombotic events? If radiation is proven to have long-lasting efficacy, should it be used for all patients undergoing angioplasty or confined only to patients with restenosis and/or other subgroups? Will radiation therapy be so effective that it will replace coronary stents, or will it always be used as an adjunct to a stenting strategy?

These questions provide a foundation for the next decade of investigation. After the past decade of failures in the struggle against restenosis, the next decade promises more success.

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Direct-to-Consumer Drug Marketing:

Public Service or Disservice?

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Abstract

Pharmaceutical industry spending on direct-to-consumer advertising has been increasing rapidly. While the primary goal of direct-to-consumer advertising is to sell drugs, supposed secondary goals include patient education and improved health. However, these benefits of direct-to-consumer advertising are unproved. Moreover, such advertising may create unnecessary tension between the patient and the patient's physician and insurer, and may divert physicians' efforts away from important patient concerns, and toward marketing-generated discussions. On the other hand, direct-to-consumer advertising may lead to patient-doctor encounters that would not have occurred otherwise. Direct-to-consumer advertising should be modified to unambiguously benefit the health-care interests of consumers and patients.

Key Words: Prescription drugs, pharmaceutical industry, marketing, advertising.

Introduction

Direct-to-consumer (DTC) marketing is a growing area of pharmaceutical industry activity. Currently, such activity is of unclear net benefit to patients. Arguments supporting DTC advertising include its informational content and patient empowerment through education. However, the primary goal of DTC advertising is to sell medication. The primary motivation is financial profit. Is DTC advertising benign, helpful, or harmful to patients? To date, the effects of DTC advertising have not been studied rigorously, although some data exist. In this essay, we discuss implications of DTC advertising and suggest alternative approaches which are more apt to support patients' interests.

Background

The pharmaceutical industry is one of the most profitable industries on the Fortune 500 list. In this high stakes arena, a single successful drug can generate billions of dollars in revenue. Research and development for failed drugs can cost billions of dollars as well. Pressures to generate revenue have led the pharmaceutical industry to direct advertising to patients in addition to health-care professionals. For some drugs, such as Claritin® and Zyban®, 90% of promotional spending is directed toward consumers (1). While spending on advertising in medical journals is decreasing, DTC advertising spending for prescription drugs is increasing rapidly. In 1996, $600 million was spent (2). By 1999, annual spending exceeded $1.5 billion (1). Drug manufacturers may find that generating consumer demand is an effective supplemental strategy to alter managed care formularies, because physicians' influence and prescribing autonomy are constrained within these plans. Some managed care organizations are responding to these pharmaceutical industry initiatives by providing physicians with guidance in dealing with patient requests for non-covered proprietary drugs.

The Food and Drug Administration (FDA) has had the authority to regulate pharmaceutical advertising since Congress gave it jurisdiction in 1962. In 1983, the FDA commissioner, re-

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For the Committee on Bioethical Issues of the Medical Society of the State of New York.

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sponding to several DTC advertisements, requested a voluntary two-year moratorium on DTC advertising, which began in October 1983. Public pressure and drug industry initiatives forced the FDA to reexamine its long-standing policy opposing DTC advertising of prescription medications. The FDA expressed reservations about the content and priority of DTC advertising, citing an inherent conflict between promotional content and objective information (3). In 1985, the FDA permitted DTC advertising under the same standards that existed for advertising to physicians, namely, fair balance and full disclosure (4). In 1997, after years of wrestling with DTC advertising, the FDA published draft guidelines for advertising directed to consumers; these guidelines stipulated truthful description of the product's indication, and a "major statement" about the associated side effects and contraindications. However, the brief summary of the drug's indication, contraindications and side effects required for promotional advertisements may be omitted if instructions are provided for how consumers can obtain detailed information about the drug, e.g., toll-free telephone number, internet web address, referring patients to pharmacists or physicians (5). Final guidelines are under development. Unfortunately, the FDA is not empowered, and does not have the resources, to require preapproval of advertisements. These deficits compromise the FDA's effectiveness in regulating DTC activity.

The pharmaceutical industry's history of noncompliance with FDA regulation of physician and consumer advertising is well documented. Wilkes et al. studied 109 full-page advertisements appearing in ten leading medical journals, along with all available references cited in the advertisements (6). They evaluated these advertisements against FDA guidelines and concluded that guidelines for balanced presentation of material were violated in 30–40% of cases. Fifty-seven percent of advertisements were found to have little or no educational value. Rothermich et al. (7) examined 94 prescription drug advertisements in three medical journals. These investigators found that health-related quality of life claims in the advertisements were usually implied and that 40% of the advertisements did not comply with FDA regulations. The FDA's Division of Marketing, Advertising, and Communication maintains a web page listing its regulatory correspondence with drug manufacturers regarding alleged violations in advertising (www.fda.gov/cder/ddmac).

Empiric information surrounding DTC advertising is limited. A survey of family physicians found a degree of ambivalence about DTC advertising, although most physicians expressed negative views. Advantages of DTC advertising cited by these physicians included patient information and the promotion of patient-doctor communication, while disadvantages included cost and misinformation (8). Ninety-five percent of these physicians were approached by patients with requests for specific prescription medications within a six-month period of learning of them.

Other studies suggest both positive and negative effects of DTC advertising on consumers. A study of 1500 subjects exposed to magazine or television advertisements for fictitious prescription drugs found that the television advertisements were more likely than magazines to promote consultation with a physician about the particular drugs. Magazine advertisements had less of an effect on consultation-seeking behavior, but were more likely to enhance the patients' view of their authority in drug decision making (9, 10). A convenience sample of 202 outpatients was surveyed after viewing a televised advertisement. This study found that patients viewing an advertisement with both promotional and risk-related product information have difficulty in learning either type of information (11). A study of 150 television commercials for over-the-counter drugs found that consumer awareness of the product was primary, education was not well integrated into the advertisement, and a casual attitude toward drug use was encouraged (12). A survey by the American Pharmaceutical Association found that about 30% of consumers who had seen a DTC advertisement asked their physicians questions about the product and a similar proportion asked their physicians about the associated health condition (13). Of those who spoke to their physician after seeing an advertisement, about one-third asked for a prescription for the advertised medication. The survey found that consumers described the advertisements as unclear, with television advertisements less useful than print advertisements. A telephone survey of 329 randomly selected California consumers found that awareness of DTC advertisements correlated with being affected by the health condition the advertised drug was developed to treat (14). This survey also found that 50% of respondents thought advertisements had to be approved by the government, 43% thought only "completely safe" medications could be advertised, and 22% believed that prescription drugs with serious side effects were restricted from advertisements. Additionally, there was a highly significant correlation between a positive attitude about DTC advertising and false confidence in how DTC advertising is regulated.

Data suggest that patients may not be upset with their physician for refusing to prescribe the advertised medication (9). Overall, the effects of television advertising on patient education and health appear mixed. On the one hand, advertisements may be unclear or misleading, while on the other hand, patients may be stimulated to seek additional information from a physician. More data are needed describing the effects of DTC-generated patient visits on doctor-patient communication, patient and physician satisfaction, and on health promotion and disease prevention activities.

Some important health concerns are addressed by DTC advertising, such as adjuvant treatment for smoking cessation and treatment of hyperlipidemia. However, as might be expected, pharmaceutical manufacturers' choices of drugs to promote appear to be governed by profit as well as by a desire to improve public health, and are limited to certain maladies and diseases. For the 12-month period ending March 1999, of the ten most promoted brands, three treated seasonal allergies, one treated male baldness, and one treated erectile dysfunction (1). Successful amelioration of these and other maladies may be important to individuals so afflicted, and pharmaceutical industry attention to symptom relief is worthy. We believe all medically recognized maladies are appropriate targets for advertising. However, the industry's choices of drugs to promote for certain maladies do not support the argument that DTC advertising serves as an important public health tool.

Major professional organizations have parallel positions on DTC advertising. The American Medical Association opposes product-specific DTC advertising of prescription medication (15). A review of several national organizations of pharmacists and the American Public Health Association found that all groups support educational advertising and all discourage medication-specific advertising (13).

Why DTC Prescription Drug Advertising Is Different from General Product Advertising

DTC prescription drug advertising differs from general product advertising because of the nature of the product and the nature of the targeted need. Health differs from typical consumer needs because: (a) health is a fundamental necessity; (b) the consumer often cannot adequately assess for the absence or presence of disease; (c) treatment requires specialized expertise; and (d) misdiagnosis, mistreatment, or nontreatment may have profound consequences. Furthermore, people who are ill are frequently rendered vulnerable to exploitation by their disease. DTC advertising targets persons with health conditions of sufficient significance to warrant physician assessment. Furthermore, these conditions are sufficiently serious to justify use of prescription medication, the subset of medications with the greatest potential for toxicity and drug-drug interactions.

DTC prescription drug advertising differs from general advertising because the former creates demand for a product: (a) that the consumer is poorly prepared to evaluate, (b) that may be inappropriate or harmful for the patient, and (c) to which consumer access is controlled by physicians.

Benefits and Harms of DTC Advertising

Evidence suggests that DTC advertising may stimulate doctor-patient communication, at least for well-educated patients (8). Through DTC advertising, patients may seek health screening, become aware of health concerns overlooked by their physician, or may raise a treatment option not considered by the physician. New opportunities for patient education may be generated. Additionally, patient inquiry about advertised medications may induce doctors to keep abreast of developments in drug therapy. Patients who discuss information from DTC advertising with their physicians may have more frequent and productive communications with them. These visits may lead to query-specific care, as well as more broadly focused health activities.

On the other hand, DTC advertising tends to stimulate patient demand for specific medications. Since the physician's efforts must always be prioritized to important patient problems, the time for reeducating and reorienting their patients' conceptions regarding inappropriate medications may not be available. When the physician advocates nontreatment, in the patient's interest, the patient may suspect unjustified refusal or even deception. These interactions may distress both physicians and patients and compromise the trusting relationship they have established. And, in this cost-conscious health-delivery environment, DTC advertising may exploit already-existing suspicion of physician interest. Further study of the doctor-patient dynamic is warranted to compare requests for specific medications with general or inexplicit requests for medications, and to compare the effects of DTC advertising on general health issues such as health screening interventions.

In some cases, DTC advertising can pose a health risk. Historically, after the release of a new medication, its use gradually increases, providing some opportunity to monitor adverse reactions. DTC advertising can generate tremendous early demand for a newly approved medication, which may expose large numbers of patients to as-yet unrecognized side effects. For example, in its first 8 months on the market, Viagra® sales reached $608 million (16). Sales have slowed after complications in patients with coronary heart disease were recognized. Similarly, troglitazone, a new oral medication for diabetes, was widely promoted until cases of serious hepatotoxicity developed.

Competition to attract and retain patients may result in efforts to increase patient satisfaction, perhaps by a readiness on the part of the physician to accommodate patient requests for medication. These requests can then fuel tensions between the physician, the patient, and a managed care organization (when involved) (1). Here, physicians balancing responsibilities to their employer with obligations of patient advocacy, face yet another profit-motivated challenge to professional credibility.

DTC advertising may foster inappropriate medication use. Data suggest that patient demand motivates inappropriate drug prescribing (17, 18). Other data suggest that both patient expectation and physician perception of patient expectation for prescription medication correlate with the issuance of a prescription (19).

Furthermore, some DTC advertising is an affront to the traditional, albeit evolving, medical contract with society. Marketing to patients implies that physicians are deficient in their responsibilities to patients, and may underprescribe medications. Furthermore, the fact that the preponderance of marketing activity for some drugs is directed to consumers suggests a trend toward diminishing the doctor-patient relationship. The industry may claim it is promoting the doctor's role by directing patients to see a doctor. However, these patient visits result from consumer demand for a product "prescribed" by the manufacturer, not the physician. The role of medicine in society and the relationship between patient and physician are worthy of reevaluation in the context of DTC advertising. However, such an analysis is beyond the scope of this discussion.

The data are clear that physicians often underutilize important medications (e.g., beta blockers for myocardial infarction, inhaled steroids for asthmatics). Variation in clinical practice is a well-recognized phenomenon, as Morris suggests, refractory to practice guidelines, educational initiatives and other interventions, because humans have a limited ability to incorporate information in decision making (20). This problem is large and complex. To our knowledge, however, there are no data showing that advertising to patients improves physicians' prescribing patterns, patient outcomes, or cost effectiveness of care. In fact, DTC advertising may lead to inappropriate and possibly harmful overuse of medications, as seen recently with heavily marketed anti-influenza medications (21).

A different kind of focus is on the horizon: pressure is slowly building for traffic in confidential medical information (22). Arguments supporting DTC advertising have been advanced to advocate targeted consumer advertising utilizing personal medical data. Some of the purported benefits of DTC advertising, i.e., patient education and better treatment choices and care, arguably, are more readily achieved if individual patients receive advertisements related to their own diagnosed conditions and current treatments. For example, a hyperlipidemic patient may receive information on lifestyle modification, medical treatment, and monitoring. However, such patients may also be poorly served. For example, a similar patient could receive advertisements promoting an antilipidemic medication as superior to the one prescribed for and being taken by the patient, leaving him or her confused and skeptical about the benefits of current treatment and the competence of the prescribing physician.

Business and Health Care Ethics

Codes of ethics for health professionals recognize the inherent vulnerability of the patient and the tension between patient autonomy and appropriate physician paternalism. These codes direct physicians to advocate for their patients, protect their patients from harm, promote patient good, serve patients as their fiduciary, and be self-effacing where personal and patient interests conflict.

Business ethics operate from a different set of premises, many of them codified in laws and regulations. In terms of marketing, ethical obligations are generalized among the target population. For example, one may argue that DTC advertising is ethical because many consumers benefit from greater awareness of specific health conditions, whereas no one is harmed because physicians control drug prescribing. Patient-directed concerns within professional ethics may not register on scales of business ethics.

Recommendations

The health benefits of DTC advertising can be achieved without many of the attendant negative effects. Public service messages describing important health conditions and their appropriate treatment(s) can better achieve the educational goals claimed by pharmaceutical advertisers. Such activity could stimulate patient-physician discussion without creating inappropriate demand, and without exacerbating tension between patients and the health system. One might argue that there is a public right to information about prescription medication. However, this information, divorced from obscuring promotional material, is widely available to consumers in innumerable books and internet web sites, from professional organizations, and from the Food and Drug Administration, as well as other governmental sources.

The Committee on Bioethical Issues of the Medical Society of the State of New York holds that DTC advertising, as presently conducted, is of unproved net benefit to the public, and may disadvantage patients and consumers. Some may argue that such advertising should not be restricted merely because of unproved net effect. But, historically, physicians have operated according to the dictum "primum non nocere." Physicians must advocate practices that unambiguously benefit their patients, whatever other social groups may endorse.

The committee therefore challenges the medical community and the pharmaceutical industry to reexamine their interrelating practices to better promote patient health and welfare. Specifically, the committee supports the following measures to improve consumer knowledge and patient care:

- It should be permissible for specific medications to be named in consumer promotions in regulated media only for nonduplicative medications, and only in conjunction with clear educational content.

- Unsolicited patient-directed prescription advertising should be prohibited.

- We agree with recommendations to enhance the FDA's ability to sanction and its authority to enforce penalties for breaches of its advertising guidelines (23). If such ability is insufficient to modify practices, we support allocation of additional resources to make possible pre-screening and approval of advertisements by regulatory bodies prior to their release and distribution. Moreover, FDA scrutiny of advertisements directed toward health care professionals and published in professional journals is desirable, because consumers increasingly access professional journals for health information.

- Professional organizations should improve efforts to foster continuing professional education, disseminate literature on evidence-based medicine and current best practice, and quickly alert physicians to important new developments (good and bad), so that physicians are better able to provide patients with state-of-the-art medical information and care. Publications which regularly offer analyses of the benefits, risks, and costs of alternative drug treatments are invaluable resources.

Clearly, DTC advertising has not been adequately studied. To improve the factual basis for regulation, and to perhaps identify additional ways to improve health, we offer suggestions toward a research agenda:

- The physician-patient relationship: How does DTC advertising affect this dynamic? Is information sharing enhanced? Does physician unwillingness to prescribe advertised medications create suspicion or distress, or does it stimulate productive health encounters?

- Public and personal health effects: How does DTC advertising affect patients' health knowledge, health practices and other behaviors, including medication compliance? What assumptions do laypersons hold about DTC advertising in terms of regulations and restrictions for advertisers, accuracy, and completeness of information and product safety?

- Clinical practice: How does DTC advertising affect medication usage, health outcomes, health-care costs and cost-effectiveness of care? How does DTC advertising affect physicians' prescribing patterns and clinical practices?

Conclusion

DTC advertising is yet another example of the challenges faced by consumers, physicians, and society as a whole, when powerful market forces confront health-care interests. While pharmaceutical companies serve a most valuable role in medical care, DTC advertising essentially is a profit-motivated activity of unproved benefit to the public. Public good requires that patients be educated, not exploited, and that professional integrity be maintained and supported. DTC advertising should be held to standards of accuracy, clarity and balance that will help realize these goals. Further studies are essential to assure that patients are being well served.

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Editorial

Educating, Informing, and Advertising:

How and Why?

SHERMAN KUPFER, M.D., EDITOR-IN-CHIEF

AN ARTICLE BY Berger, Kark, Rosner, et al. entitled "Direct-to-Consumer Drug Marketing: Public Service or Disservice?" appears in this issue of *The Journal.* The manuscript resulted from discussions of the Committee on Bioethical Issues of The Medical Society of the State of New York. It deals with some very important aspects of the delivery of health care by providers, their responsibilities to patients, and the receipt of these services and materials by patients as individual consumers and/or as groups of consumers.

The blinded manuscript was sent for peer review upon its receipt. There was a wide range of opinion expressed by the reviewers in their responses, along with many comments and suggestions. Their initial general feeling was that a revised manuscript which addressed these comments and incorporated the suggestions would merit reconsideration of publication in *The Journal.* This information was transmitted to the authors, who undertook to revise and resubmit the manuscript. All of the reviewers noted that the revised manuscript was better. The editorial staff agreed with that assessment, but now some concern and sentiment were expressed regarding the appropriateness of publishing, in *The Journal*, a manuscript which outlined a position of an agency of The Medical Society of the State of New York. Others maintained that an institutional, agency, or commercial affiliation or association of an author, or group of authors, should not bar consideration of their manuscript for publication in *The Journal.* Careful attention must be given to the peer reviews and possible conflicts of interest to assure that *The Journal* serves as a forum for important information on health care. Editorial decisions regarding publication must be based on the quality of the scholarly presentation. In line with this latter view, the authors were contacted again to query their relationship as a group to the Medical Society. I have been informed that the Medical Society has neither commented on, nor endorsed, the positions of the authors as described in their paper.

It is, perhaps, easiest to start by defining the role of the pharmaceutical and health equipment-device industries as driven primarily by the profit motive and secondarily by a stated desire to improve public health. In and of itself, and within reason, the profit motive is not necessarily bad, since without such a stimulus, there would be little or no incentive to stay the course in the search for new and better items to market. But it is not hard to harbor anxieties and suspicions when advertising claims of superior effectiveness and benefit-cost ratios are primarily directed toward patients who are unable to evaluate whatever scientific evidence may be included in the written or verbal presentation. Coverage and information on health-care developments offered by the general lay press also may not provide a balanced view to the patient (1, 2). So, whose responsibility is it to provide the elements necessary for an informed decision? Freedom of speech is a fundamental right in our society, but this has had to be tempered by various governmental regulatory agencies, including the Food and Drug Administration (FDA), to protect the public welfare. The authors suggest that drug advertisements be subject to pre-screening and approval prior to their release and that sanctions be applied when guidelines are disregarded. There is little or no evidence to suggest whether this can be implemented, and how effective such a program might be. With respect to the goal of improving public health, the authors conclude that the evidence does not support the view that direct-to-consumer (DTC) advertising is an important tool. On the other hand, targeting advertisements to individual patients with specific information that recommends alternative drug choices for their illnesses, may serve to broaden their horizons, but it comes at the price of unwarranted, if not illicit, traffic in confidential medical records.

The professional community of health-care practitioners and clinical researchers has a plethora of tools by which information can be and is transmitted. These tools include journals (printed and electronic); society and association meetings; and meetings sponsored by academic health centers, medical schools, hospitals, etc. Continuing education is one of the basic tenets of professionalism, and a medical degree, a license to practice, and board certification as a specialist obliges the recipient to maintain and prove current proficiency. There is little documentation regarding how well this obligation is being met, but conventional wisdom suggests that much time, effort, and money are being expended. With respect to transmitting the new information developed in the basic sciences and its evaluation by clinical scientists and practitioners, a multitude of resources including the aforementioned written and electronic scientific (specialty) journals, and various meetings do exist. Increasingly, patients and the media also access these professional sources for information on health care.

The more "sensational" the information is or can be made, the more rapid is its announcement and distribution to the general public. This, of course, creates great pressure on individual physicians who are asked by their patients how these new developments relate to or impact on their own treatment. It is unreasonable to expect a given physician to be instantly knowledgeable about the specific details of the new "evidence" presented in any of the given formats mentioned above. Thus, the authors' recommendation that physicians should be alerted quickly to new developments (good and bad) would be both desirable and helpful.

This certainly would be a proper role for The Medical Society of the State of New York to assume, to develop, and to implement. The Society, however, discontinued its journal of many years without providing an alternative means of transmitting, under its sponsorship, important and timely expert professional recommendations to its membership. The Society should consider developing its web site and e-mail capabilities, and its bulletin, to accommodate the transmission of this information to its members. The Society could then ensure the distribution of reliable, balanced, and unbiased health-care information assembled by experts devoid of conflicts of interest. Another worthy goal which the Society could accomplish would be to reduce the long lag time in implementing valid diagnostic and therapeutic modalities (or in discarding ineffective ones), despite abundant supporting evidence already published or presented.

One of the major factors in the editorial decision to publish this paper in *The Journal* was a need to call attention to the issues surrounding direct-to-consumer advertising in health care, as a purported mechanism for patient education. What is critical in any meaningful conclusion regarding the effects of this sort of advertising is the rigor employed by the relevant studies. There is little doubt that more and better research must be carried out. Whether the Committee or the Medical Society should become engaged in sponsoring and/or conducting this research has yet to be addressed, but the Medical Society must face up to its responsibility to its members to help them serve the best interests of their patients. In the last analysis, the profession is obliged, and is best positioned, to transmit expert and comprehensible information about personal and public health to all patients and their respective communities. The endorsement of a recommendation by a medical society must be firmly grounded on the weight of the evidence. While it has been said that progress is our most important product, surely one must be able to evaluate, appreciate, and recognize the quality of the evidence before becoming committed to, or convinced of, any claim of benefit. Much has been done, but the profession, its societies, and their members must learn how to better traverse the new avenues and technologies if the "Golden Fleece" sequestered in the burgeoning information database is to be captured.

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The Mount Sinai Hospital Clinicopathological Conference:

A 45-Year-Old Man with Pompe's Disease and Dilated Cardiomyopathy

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Abstract

This is an unusual case of a 45-year-old man, born in Ecuador, with evidence of profound left ventricular dysfunction, dilated cardiomyopathy and marked myocardial hypertrophy. Preceding events were advanced atrioventricular block (necessitating pacemaker implantation) and atrial flutter.

The diagnosis of Pompe's disease was established by endomyocardial biopsy and appropriate staining, which indicated abnormal glycogen storage.

Key Words: Dilated cardiomyopathy, heart block, glycogen storage disease, Fabry's disease, Pompe's disease, Chagas' disease, congestive heart failure, ventricular dysfunction

Case Presentation

A 45-YEAR-OLD MAN was admitted to the hospital for progressive heart failure. The patient had felt well until he was in his early thirties. He had been able to compete in multiple triathlons and other sporting events. At the age of 31, he developed several episodes of exercise-induced syncope, and his electrocardiogram (ECG) revealed advanced atrioventricular heart block (Fig. 1). A dual-chamber pacemaker was implanted and the patient resumed his athletic activities.

Eleven years later, he was admitted to the hospital with acute onset of abdominal pain and nausea. An extensive investigation revealed a renal artery thrombus to be the cause of his symptoms. A transesophageal echocardiogram was performed to rule out a cardioembolic source. The test revealed no thrombi or vegetations within the heart or aorta. The patient's left ventricular ejection fraction was noted to be moderately decreased, at approximately 40%. There was marked concentric left ventricular hypertrophy, with a diastolic thickness of the interventricular septum of 20 mm (normal 8–11 mm). The left ventricle and atrium were moderately dilated. A search for a hypercoagulable state (antiphospholipid antibodies, activated protein C resistance, protein C, protein S and antithrombin 3 deficiencies) revealed no abnormalities. The patient was started on warfarin therapy and discharged from the hospital.

He remained on anticoagulation therapy and felt well until the age of 44, when he experienced an episode of acute shortness of breath and palpitations. An electrocardiogram showed atrial flutter with a rapid ventricular response related to ventricular tracking (Fig. 2). Both the arrhythmia and his symptoms abated spontaneously within twenty-four hours.

Nine months later, the patient began to experience a marked decrease in his exercise tolerance and significant dyspnea on exertion, and he again experienced symptomatic atrial flutter with shortness of breath, requiring DC cardioversion, after which he reverted to regular sinus rhythm. A transesophageal echocardiogram (Fig. 3) was performed. Left ventricular ejection fraction had decreased to 9% and all four chambers of the heart were severely dilated. Also noted was a prominent fibrosed left ventricular apical endocardium. The patient was subsequently treated with digoxin, war-

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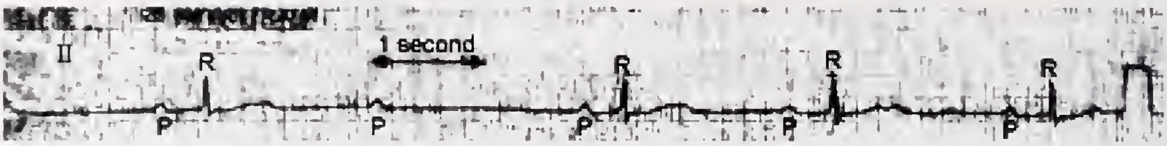

Fig. 1. Electrocardiogram of patient at age 31, showing sinus bradycardia and advanced atrioventricular block.

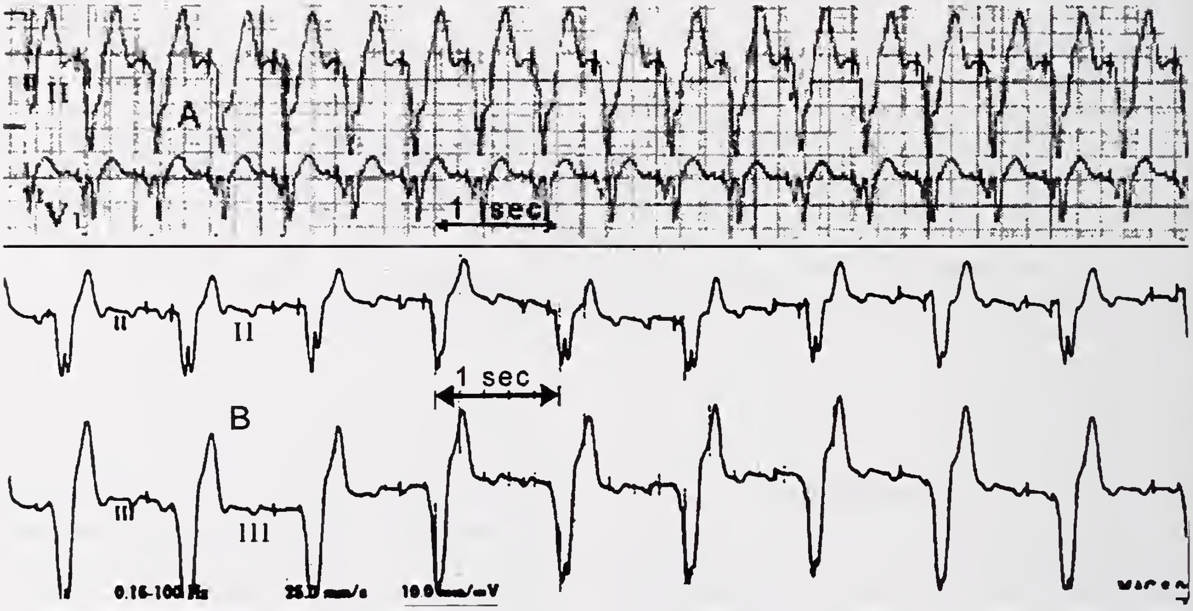

Fig. 2. A. Electrocardiogram of patient at age 44, showing atrial flutter with rapid ventricular response due to ventricular tracking. **B.** Atrial flutter is seen after pacemaker had been programmed at a slower rate.

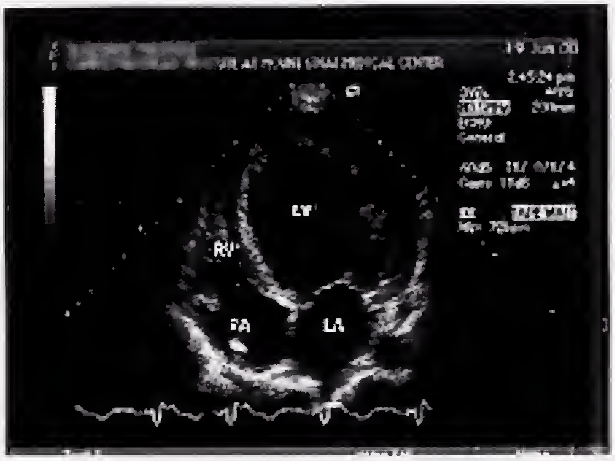

Fig. 3. Echocardiography showing severe left ventricular dilatation and fibrosed apical endocardium.

farin, an ACE inhibitor, and furosemide, and admitted to the hospital.

The patient had lived in Ecuador until he was 10 years old, at which time his family moved to the United States. He worked as a computer analyst. He drank a can of beer every two weeks or so, and denied alcohol abuse, smoking, or use of illicit drugs. His parents were first cousins. There was no family history of cardiac disease, hypertension, diabetes, sudden death, or arrhythmias, and there were no apparent risk factors for infection with human immunodeficiency virus. He had not experienced any recent viral or flu-like illness.

On admission to the hospital at this time, physical examination demonstrated minimal crackles at the bases of the lungs, an S3 gallop, a displaced apical impulse, and trace pedal edema. The patient's blood pressure was 128/76 mm Hg, pulse 68 bpm and respiration 16/min. A chest X-ray showed an enlarged heart without pulmonary congestion. Laboratory tests on admission, including thyroid-stimulating hormone, were within normal limits. An electrocardiogram showed an atrioventricular-paced rhythm (Fig. 4). Coronary angiography revealed normal coronary arteries. Left ventricular cine-angiography revealed severely reduced global left-ventricular function. A diagnostic procedure was performed.

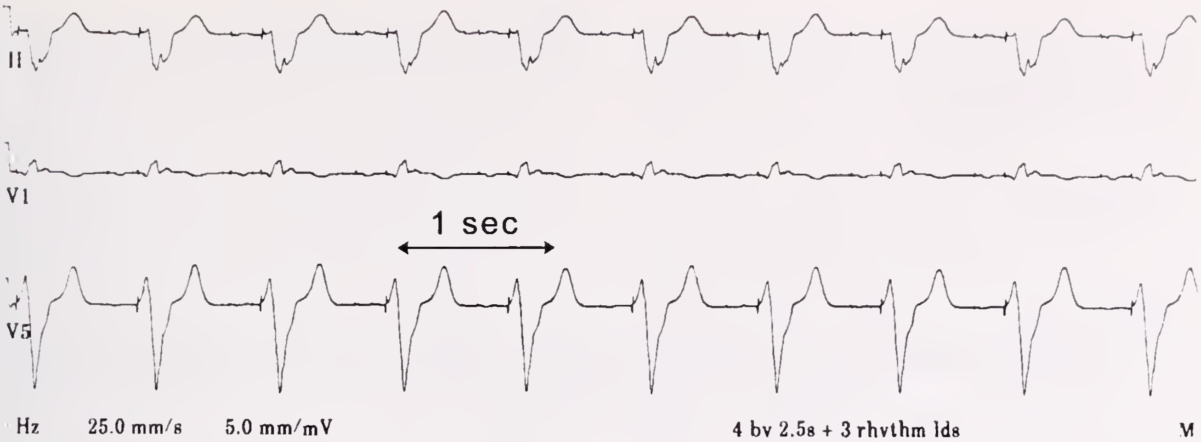

Fig. 4. Electrocardiogram showing atrioventricular-paced rhythm.

Discussion

Principal clinical features in this 45-year-old man included:

- Stokes-Adams attacks due to sinus bradycardia and advanced atrioventricular block, which became manifest at the age of 31
- A dilated cardiomyopathy, the first signs of which were detected ten years later, when he experienced a systemic thromboembolic event
- Atrial flutter
- A notable absence of primary involvement of extracardiac organ systems by a disease process

Two features set this case aside from typically presenting idiopathic dilated cardiomyopathy (DCM). One is the appearance of a complete atrioventricular block many years before the onset of cardiomyopathy. The other is the significant concentric myocardial hypertrophy noted on the first echocardiogram performed three years prior to the last admission, where an interventricular wall thickness of 20 mm with moderate left ventricular dysfunction was described. It may be tempting to attribute this finding to this patient's athletic activities. However, a vast majority of competitive athletes have a left ventricular wall thickness of 12 mm or less; only a few have a wall thickness of 12 to 16 mm. A left ventricular wall thickness of 20 mm is well within the hypertrophic cardiomyopathy range (1).

Did this patient have a hypertrophic cardiomyopathy which progressed into a dilated one? This seems unlikely, since a late dilated phase is not part of the natural history of hypertrophic cardiomyopathy (2).

The process we are looking at is therefore one which involves the conducting system early in its course, presents with a thick but poorly contracting myocardium, and eventually progresses to a DCM. We will concentrate on the differential diagnosis of DCM while taking these other features into consideration.

DCM was defined by a World Health Organization task force in 1995 as dilatation and impaired contraction of the left ventricle or both ventricles (3). In order to identify a primary myocardial process as the cause, extrinsic forces which may cause myocardial dilatation must be ruled out. These include hypertension, coronary artery disease, valvular heart disease and congenital heart disease. For this patient, coronary angiography was normal and echocardiography showed no evidence of primary valvular disease or a cardiac shunt.

Patients with DCM most commonly present with heart failure which is typically advanced (90% are classified as New York Heart Association class III or IV). Less common modes of presentation include chest pain and asymptomatic cardiomegaly detected incidentally. Only 1.5–4% have a thromboembolic event as their first manifestation, as in this case (4).

DCM is believed to be the end result of multiple toxic, metabolic, infectious and inflammatory insults to the heart (Table). Sustained tachycardia is also an important reversible cause of DCM. This patient presented with supraventricular tachycardia, but the termination of the arrhythmia was not associated with improved left ventricular function, a feature common to all patients with tachycardia-

TABLE
Differential Diagnosis of Dilated Cardiomyopathy

Extramyocardial Disease
- Hypertension, coronary artery disease, valvular heart disease, congenital heart disease, coronary artery bypass surgery

Intrinsic Myocardial Disease
- **Toxins/Drugs**
  - Ethanol*, chemotherapeutic agents, cobalt*, antiretroviral agents*, phenothiazines*, carbon monoxide*, lead*, cocaine*, mercury*, radiation
- **Metabolic causes**
  - Nutritional deficiency: thiamine*, selenium*, carnitine*
  - Endocrine: hypothyroidism*, thyrotoxicosis*, acromegaly*, Cushing's disease, pheochromocytoma*, diabetes mellitus
  - Electrolyte abnormalities: hypocalcemia*, hypophosphatemia*
- **Uncontrolled tachycardia***
- **Infectious causes**
  - Viral: Coxsackie B3, CMV*, HIV
  - Rickettsial: Lyme disease
  - Bacterial: diphtheria*
  - Mycobacterial
  - Fungal
  - Parasitic: toxoplasmosis*, trichinosis, Chagas' disease
- **Collagen vascular disease**
  - Progressive systemic sclerosis, SLE, dermatomyositis, rheumatoid arthritis, polyarteritis nodosa, Wegener's granulomatosis
- **Other inflammatory**
  - Hypersensitivity myocarditis, giant cell myocarditis, peripartum myocarditis
- **Neuromuscular causes**
  - Duchenne's muscular dystrophy, Becker's muscular dystrophy, facioscapulohumeral dystrophy, Erb's limb-girdle dystrophy, myotonic dystrophy, Friedreich's ataxia
- **Infiltrative causes**
  - Storage diseases: hemochromatosis, Fabry's disease, glycogen storage disease
  - Sarcoidosis
  - Amyloidosis
  - Neoplasm
- **Idiopathic**
- **Familial**

* Denotes potentially reversible cause.
Abbreviations: CMV — cytomegalovirus, HIV — human immunodeficiency virus, SLE — systemic lupus erythematosus

induced cardiomyopathy (5), nor did it reverse the continuing deterioration in systolic function. Thus, the tachycardia is an unlikely cause of his cardiomyopathy. Of the many toxins and drugs implicated in DCM, alcohol is particularly common and should always be considered. Alcoholic cardiomyopathy may account for as many as one third of all DCM cases in Western countries. Mechanisms involved include a direct cardiotoxicity of alcohol, nutritional deficiency of thiamine and, in rare cases, contamination of beverages with cardiotoxins such as cobalt. Detection may be difficult when patients deny or underestimate alcohol consumption. Evidence of alcoholic damage to the liver or nervous system is frequently absent. Concurrent alcoholic myopathy may suggest the diagnosis of alcoholic cardiomyopathy. Abstinence may reverse alcoholic cardiomyopathy, but only if instituted sufficiently early in its course (6).

Nutritional deficiencies, endocrine abnormalities and electrolyte disturbances may cause reversible forms of cardiomyopathy. For this patient, thyroid function tests were normal and no electrolyte imbalance was noted on routine blood testing.

Of the many infectious agents that may cause DCM, enteroviral infection, particularly with Coxsackie B3, is the most commonly implicated. Myocarditis is a frequent finding in biopsy samples from patients evaluated for DCM (7), and these patients have often had a recent "viral infection." Several studies using the polymerase chain reaction to look for enteroviral genome in myocytes have failed to provide any evidence of persistent viral infection in DCM (8, 9). The role of enteroviral infection in DCM remains controversial.

HIV infection is emerging as an important contributor to DCM, both as a result of direct viral infection of myocytes and cardiotoxicity of antiretroviral medications. Cardiomyopathy is usually found in advanced HIV infection, the most important contributing factor being the inverse of the CD4 cell count (10). However, HIV cardiomyopathy is unlikely in a patient who has had progressive cardiomyopathy for more than three years with no other evidence of HIV infection.

This patient spent the first ten years of his life in Ecuador, making Chagas' disease an important consideration, since Chagas' is endemic in all Latin American countries. Five percent of immigrants from South America to the United States are seropositive for *Trypanosoma cruzi* (11). The disease is characterized by an acute illness, usually in early childhood, often mild enough to be forgotten. This is followed by an asymptomatic phase, which may last for decades. Ultimately, 10–30% of patients will develop chronic Chagas' disease, which most commonly involves the heart. Chagas' favors the cardiac apex, and the finding of an apical scar or aneurysm is suggestive of this disease. In the patient under discussion, echocardiography demonstrated extensive apical endocardial fibrosis, which may be consistent with Chagas'. The conducting system is commonly affected in Chagas', the classic combination being right bundle branch block and left anterior hemiblock. Complete atrioventricular block can also occur. However, Chagas' disease would not explain the long latency between onset of conduction block and cardiomyopathy or the myocardial hypertrophy noted in this patient.

Although a variety of collagen vascular diseases can cause DCM, the absence of any systemic involvement in this patient makes these entities unlikely. Muscular dystrophies, another etiology of DCM, can be safely ruled out in view of this patient's exercise capacity. Of the 50% of DCM cases which continue to be defined as idiopathic (7), 20% have at least one first degree relative who has DCM, and it can now be demonstrated that more than 30% have a genetic mutation associated with DCM (12). Several of these mutations have recently been characterized. Patients are usually 20–50 years old at presentation, the familial nature of the disease often remaining unsuspected until another family member is diagnosed. In contrast to mutations causing hypertrophic cardiomyopathy, which involve components of the sarcomere, mutations causing DCM involve components of the cytoskeleton. These structures serve to anchor the sarcomere to the myocyte membrane, and their disruption uncouples sarcomeric contraction from shortening of the entire myocyte, thus impairing systolic function. Of particular relevance to this case are mutations in lamin A and C, which are components of the nuclear membrane. In the families studied by Fatkin and colleagues, 54% of affected individuals required placement of a pacemaker due to high-degree atrioventricular block (13). However, mutations in lamin A/C are inherited in an autosomal dominant manner with high penetrance, so the absence of a family history would be difficult to explain. A *de-novo* mutation is still a possibility, although it would not account for the myocardial hypertrophy seen in this patient.

Infiltrative causes of DCM merit special consideration in this case. An infiltrative process can involve the conducting system early in its course. Myocardial thickening may be caused by infiltration (so-called pseudohypertrophy), but in contrast to hypertrophic cardiomyopathy, systolic function is impaired. With continued deposition of pathologic matter and replacement of functional myocytes, DCM will ensue.

Of the storage diseases involving the heart, hemochromatosis is by far the most common. Cardiomyopathy is the presenting feature in 15% of these patients, with dilatation being more common than a restrictive pattern (13, 14). Conduction abnormalities are also common; in one study iron overload was found in 2% of 232 men requiring a pacemaker for idiopathic high-grade atrioventricular block (15).

Fabry's disease is X-linked and usually presents with angiokeratomas, corneal opacities and renal disease. However, a variant with manifestations limited to the heart may occur when residual activity of the enzyme alpha-galactosidase A is present (16). Deposition of ceramide trihexoside may mimic hypertrophic cardiomyopathy (17). Mitral valve thickening and prolapse are also common. DCM has only rarely been described with Fabry's disease. Pre-excitation is the common conduction abnormality, and AV block is very rare (18). Taken together, these features make Fabry's an unlikely diagnosis in this case.

Glycogen storage diseases (GSD) are rare. Type II GSD (acid maltase deficiency) involves the heart and is usually fatal before the age of two years. Partial enzymatic activity is responsible for the adult onset form of this disease, but these patients have predominantly skeletal myopathy; clinically significant heart disease is uncommon (19). Few patients have been described with cardiomyopathy, conduction abnormalities and lysosomal glycogen deposits similar to type II GSD but with normal acid maltase activity (20).

Sarcoidosis is an infiltrative granulomatous disease of unknown etiology. Five percent of patients have clinically apparent cardiac involvement, which may be the only manifestation of the disease. Involvement of the conducting system is common and sudden death may be the presenting symptom (21). The cardiomyopathy of sarcoidosis may be restrictive or dilated, and pseudohypertrophy is rare.

Amyloidosis involves the heart in one third of patients with AL amyloidosis and 25% of those with familial disease. Echocardiographic features suggestive of amyloidosis include myocardial thickening (coupled with low voltage on ECG), a sparkling appearance of the myocardium, and interatrial septal thickening (22). Conduction abnormalities are common. The presence of a highly echogenic myocardium is 87% sensitive and 81% specific for this diagnosis (22), but was not described in our patient. Also, amyloidosis is a disease of the elderly and is unlikely to present at the age of thirty.

A recent publication from the Johns Hopkins cardiomyopathy service reported on 1,278 patients, the single largest series with DCM to date (7). These patients underwent a basic clinical work-up, laboratory studies (including thyroid function tests and iron studies when appropriate) and endomyocardial biopsy. After this extensive investigation, 51% were designated as having idiopathic DCM. The most frequent specific diagnosis was myocarditis (9.2%). Of the infiltrative disorders, amyloidosis was diagnosed in 3.2%, sarcoidosis in 1.3% and hemochromatosis in 0.7%. While clearly subject to referral bias, this report demonstrates the utility of endomyocardial biopsy in reaching a specific diagnosis in DCM.

In summary, we believe that the sequence of atrioventricular block, pseudohypertrophy and DCM is most compatible with an infiltrative cardiomyopathy. Possible etiologies include sarcoidosis, hemochromatosis, and an atypical form of GSD. The diagnostic procedure performed was probably an endomyocardial biopsy.

Pathological Findings

The hematoxylin and eosin (H&E) stain of a right endomyocardial biopsy showed severely vacuolated cytoplasm devoid of myofibrils (Fig. 5). A PAS stain revealed dark-staining, coarse, granular inclusions in the cytoplasm of the myocytes (Fig. 6), which disappeared on predigestion with diastase (Fig. 7), proving that they are glycogen. Electron microscopic examination showed lamellar and granular inclusions in the cytoplasm at nuclear poles. Similar inclusions are also seen within interstitial macrophages and capillary endothelial cells. The nature of these inclusions in macrophages is largely granular.

The microscopic and ultrastructural features are consistent with a glycogen storage disease, probably Pompe's disease. The late onset form of Pompe's disease was first recognized in 1965. This autosomal recessive disorder is characterized by deficiency of acid alpha-1, 4-glucosidase, a lysosomal enzyme that catabolizes the breakdown of glycogen, thus resulting in accumulation of glycogen in the lysosomes in the cytoplasm. In cardiac tissue, the result is hypertrophy and vacuolization of myocytes.

The only other entity to be considered in pathologic differential of this patient is Fabry's disease, a storage disease, characterized by deficiency of alpha-galactosidase. The result is an accumulation of glycosphingolipids in the hypertrophied vacuolated myocytes, with myofibrillary disorganization. The clinical findings, such as angiokeratomas, corneal opacities and nervous system disorders, together with enzyme assays in skeletal muscle biopsies, should help differentiate the two entities.

Alpha-galactosidase activity was normal in this patient. He is unwilling to undergo a skeletal muscle biopsy at this time. GSD clinically restricted to the heart and presenting in adulthood is extremely rare. In the infrequently reported cases of Pompe's disease in adults, skeletal my-

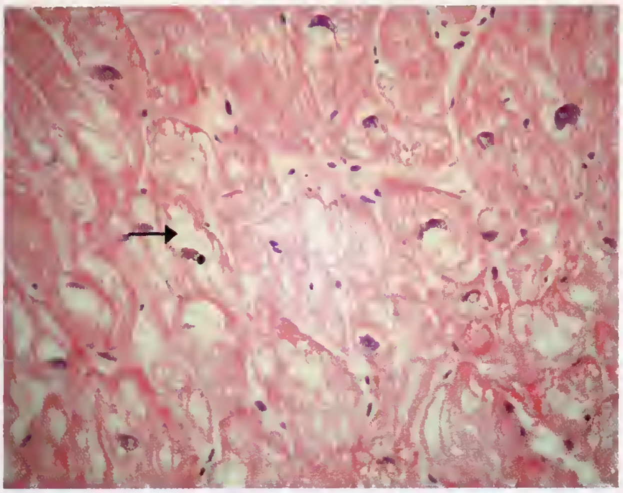

Fig. 5. Endomyocardial biopsy showing vacuolated myocytes (arrow) (H&E stain, 20x).

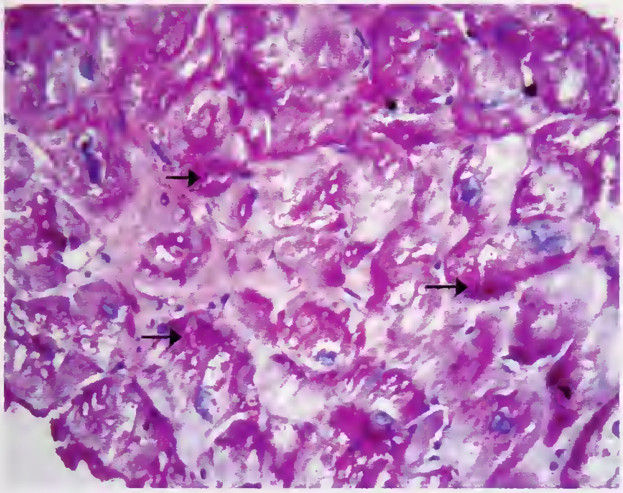

Fig. 6. Endomyocardial biopsy showing dark, coarse, granular inclusions in cytoplasm (arrows) (PAS stain, 20x).

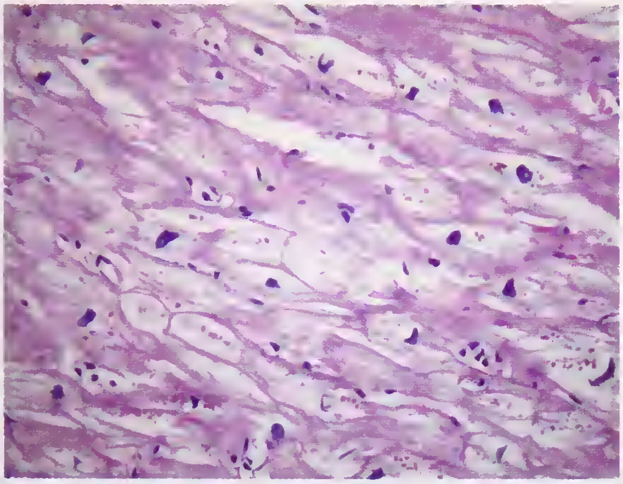

Fig. 7. After pre-digestion with diastase, cytoplasmic inclusions disappear (PAS stain, 20x).

opathy predominates. We are aware of only one similar report in the medical literature (20).

Follow-up

The patient is seen periodically. He continues to be physically active in athletic activities, including swimming and jogging. His cardiac function, however, is slowly deteriorating. His liver function tests and skeletal muscle function are normal. Thus, the metabolic defect appears to be confined to the cardiac muscle. The patient will be a candidate for cardiac transplantation in the near future if skeletal muscle and liver biopsies verify the absence of glycogen storage in these organs.

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Toxemic Shock, Hematuria, Hypokalemia, and Hypoproteinemia in a Case of Cutaneous Anthrax

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Abstract

A 20-year-old woman who had daily contact with domestic herbivores presented with a painless and pruritic lesion in her neck; the lesion ulcerated to a black necrotic eschar from which *Bacillus anthracis* grew. Rapidly expanding edema at the site of the ulcer was followed by shock, hematuria, hypokalemia, and hypoproteinemia. The latter symptoms — unusual for cutaneous anthrax — responded to intravenous penicillin therapy.

Key Words: Anthrax, hypokalemia, hypoproteinemia, isolated hematuria, toxemic shock.

Introduction

Anthrax is a worldwide infectious disease of domestic and wild herbivores; humans may become infected too when exposed to the infected animals or their products (1 – 6). *Bacillus anthracis* exotoxins mediate most of the symptomatology, causing extensive edema in cutaneous anthrax, and a clinical syndrome reminiscent of septic shock in the visceral form (7, 8). Cutaneous anthrax may be associated with a mortality of 10 – 20% (4), but there is only one prior case report in which it was associated with toxemic shock (9). To the best of my knowledge, this is the second reported case in which toxemic shock was present, and the first in which the patient developed hematuria, hypokalemia and hypoproteinemia.

Case Report

A 20-year-old Iranian village-woman who had daily contact with sheep and goats presented with a pruritic and painless lesion on the right side of her neck. In two days the lesion ulcerated and evolved into a black necrotic eschar. Progressive edema, starting from the site of the ulcer, extended rapidly to the face, neck, shoulders, chest, and breasts. Due to increasing shortness of breath, she was referred to the Nemazee Hospital of Shiraz University of Medical Sciences, where she was found to be disoriented. Her systolic blood pressure was 30 mm Hg, her pulse rate 120 /minute, her respiration rate 27/minute, and her rectal temperature normal. Visible on the right side of her neck was a round ulcer measuring 2 cm, with black necrotic center, raised borders and small satellite vesicles around it, along with massive, non-pitting brawny edema of face, neck, shoulders, and upper part of the chest wall. An arterial blood gas analysis showed pH of 7.20, CO_2 of 12 mEq/L, P_{CO2} of 24 mm Hg, and P_{O2} of 100 mm Hg. A chest X-ray was normal and electrocardiogram disclosed sinus tachycardia. Central venous pressure (CVP) was 1 cm saline. Intravenous penicillin G (4 million units every 6 hours) and intravenous fluids were started. After 2 L of intravenous normal saline, her blood pressure increased to 60 – 80 mm Hg and her CVP to 2 – 3 cm saline, and she became oriented to time, person and place. Thereafter, intravenous fluid therapy was administered at a rate to keep CVP about 3 cm saline.

A large, encapsulated gram-positive rod consistent with *Bacillus anthracis* was demonstrated in scrapings taken from necrotic tissue. Admission laboratory test results were: hemoglobin (Hb) 18.4 g/dL, white blood cell (WBC) count 27,500 mm^3 (80% polymorphonuclear cells, 17% lymphocytes, and 3% bands), and platelet count 113,000 mm^3. Liver function tests were: total serum protein 4.6 g/dL, albumin 1.8 g/dL, AST 38 U/L, ALT 23 U/L, total

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bilirubin 1.1 mg/dL, and alkaline phosphatase 170 U/L. Coagulation profile disclosed the following results: prothrombin time 21 seconds with control of 13 seconds, activated partial prothrombin time 49 seconds (normal 32–46 seconds), fibrinogen level 37.5 mg/dL (normal 200–400 mg/dL), and fibrin degradation product (FDP) 30 mg/dL (normal 5–9 mg/dL). Blood urea nitrogen (BUN) was 40 mg/dL (normal 10–20 mg/dL), with concomitant serum creatinine of 0.9 mg/dL. Serum sodium was 137 mEq/L and serum potassium was 4.6 mEq/L.

On the first hospital day, the patient passed 1.5 L of tea-colored urine which disclosed 3+ blood, and many normal-looking red blood cells/HPF with no protein or casts. Thereafter, repeated urinalysis disclosed hematuria, the severity of which gradually decreased. Eventually, the hematuria disappeared during the second week of hospitalization.

By the second hospital day, blood pressure had increased to 90 mm Hg and CVP had risen to 3 cm saline. On the 3rd day, a serum potassium level of 1.8 mEq/L was reported, while the concomitant urine potassium level was 29 mEq/L. Intravenous potassium chloride 20 mEq/hr was then started. This dose was reduced to 60 mEq/day when serum potassium concentration became normal, on the 4th day. At that time, the hemoglobin level and platelet count dropped to 9.4 g/dL and 50,000/mm^3 respectively, but the WBC count increased to 37,500/mm^3. Repeated throat, urine, stool and blood cultures were negative, but the wound cultures grew *Bacillus anthracis*. Complement (C3, C4, CH50) levels were normal. Antibodies for hepatitis B and C viruses, antinuclear antibody, VDRL, and ANCAs were negative. Creatine phosphokinase and lactate dehydrogenase were normal (59 U/L and 170 U/L respectively). Ultrasonography and CT scan of abdomen and pelvis were normal. During 14 days of penicillin therapy, edema gradually disappeared and the neck ulcer evolved into a crusted black lesion. Four weeks after the patient's discharge from the hospital, her laboratory results were: platelet count 130,000/mm^3, serum potassium 4 mEq/L, total serum protein 6.9 g/dL, albumin 3.7 g/dL, and normal urinalysis. Her physical examination, urinalyses, and abdominal and pelvic sonography have remained completely normal during one year of follow-up.

Discussion

In visceral anthrax, extensive edema, as a result of capillary wall dissolution and venous obstruction (induced by *Bacillus anthracis* toxins), may lead to systemic shock and death (7, 8). In contrast, circulatory shock is very rare in cutaneous anthrax and has only been the subject of one case report (9). Coexistence of hemoconcentration, pre-renal azotemia (BUN/creatinine ratio > 20), and massive edema on admission, associated with repeated negative blood cultures, suggests that *Bacillus anthracis* toxin induced leakage of intravascular fluid into the interstitial space, causing severe volume depletion and circulatory shock.

To the best of my knowledge, hematuria has not been reported previously in patients with cutaneous anthrax. Hematuria was repeatedly found in this patient but disappeared gradually within two weeks. The patient had not been catheterized, and no other obvious cause for hematuria was discovered. It is possible that platelet thrombi induced by *Bacillus anthracis* resulted in renal vein thrombosis and/or hematuria of glomerular origin; but absence of proteinuria, dysmorphic red blood cells and red cell casts makes hematuria of glomerular origin very unlikely. However, the sequential occurrence and disappearance of hematuria following circulatory shock, along with low fibrinogen, high FDP, thrombocytopenia, and prolonged prothrombin time strongly suggests that disseminated intravascular coagulation was the underlying mechanism for the hematuria.

Hypoalbuminemia has been reported previously in a patient with cutaneous anthrax and toxemic shock (9). This is the second reported case of cutaneous anthrax with hypoalbuminemia and the first one in which hypoproteinemia developed. The underlying mechanism(s) of hypoproteinemia in this case is not clear. There was no evidence of liver cirrhosis, chronic viral hepatitis, malnutrition, glomerulonephritis, generalized weeping skin disease, or protein-losing enteropathy. Coexistence of extensive non-pitting edema, severe hemoconcentration and pre-renal azotemia suggests that intravascular protein leaked through capillary endothelium damaged, apparently reversibly, by *Bacillus anthracis* toxins.

This is also apparently the first reported case of cutaneous anthrax in which severe hypokalemia developed. Given that the patient's urine potassium concentration was 29 mEq/L in the absence of massive diuresis, her hypokalemia cannot be attributed to renal potassium loss or low potassium dietary intake.

The present case emphasizes that patients with cutaneous anthrax can develop *Bacillus anthracis* toxin-induced circulatory shock that may be associated with hematuria, hypokalemia and hypoproteinemia. Prompt recognition and treatment is essential.

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Wernicke's Encephalopathy in a Non-alcoholic Man:

Case Report and Brief Review

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and Fred Rosner, M.D.[3,4]

Abstract

Wernicke's encephalopathy, a serious neurological disorder caused by thiamine deficiency, is most commonly found in chronic alcoholics. We present a typical case of Wernicke's encephalopathy in a non-alcoholic man. Our patient presented with altered mental status, slurred speech, fever, vomiting and headache of one-week duration. An infectious etiology of the symptoms was ruled out by spinal fluid cultures. The patient improved dramatically within 24 hours of administration of thiamine.

Key Words: Wernicke's encephalopathy, thiamine, chronic alcoholism, malnutrition, glucose.

Introduction

Wernicke's encephalopathy (WE) is a serious neurological disorder caused by thiamine deficiency and is most commonly found in chronic alcoholics (1, 2). Typically, patients have the "classic triad" of symptoms: oculomotor abnormalities, gait disturbance and global confusional state. However, some patients may not exhibit this triad. The diagnosis is then based on clinical suspicion and rapid reversibility of symptoms after administration of thiamine, or autopsy demonstration of the characteristic lesion (3, 4). We report a case of Wernicke's encephalopathy in a non-alcoholic man.

Case Presentation

A 34-year-old African-American man presented with altered mental state, fever, slurring of speech, vomiting and headache of one-week duration. The patient denied alcohol or drug abuse, protracted vomiting, starvation, hospitalizations or abdominal surgery and indicated that he ate a normal diet. He also denied any history of sexually transmitted diseases or promiscuity. He had had occasional headaches, but had never been seen by a doctor for this complaint. He claimed to be well otherwise. On examination, the patient was alert, but disoriented. His temperature was 102°F; his pulse and blood pressure were normal. He had bilateral ophthalmoplegia with vertical nystagmus, weakness of both lower extremities and gait ataxia. There was no neck rigidity or tenderness. No other focal neurological deficit was present. Complete blood count and serum electrolytes, including magnesium, were within normal limits. The liver function tests showed normal enzymes and serum bilirubin levels with a low normal albumin.

In view of the normal hemoglobin level (14.9 g/dL), serum folate was not done. Urine toxicology was negative. Although the patient declined to have an HIV test, he had normal CD4 counts with a normal CD4/CD8 ratio. Computerized tomography (CT) scan and magnetic resonance imaging (MRI) of the brain were normal. The patient was admitted to the intensive care unit with the differential diagnoses of meningitis, cerebrovascular event or Wernicke's encephalopathy. He was empirically given cephtriaxone, vancomycin, and acyclovir because of fever, vomiting, altered mental state and lower extremity weakness, which suggested the possibility of meningitis or encephalitis. Cerebrospinal tap results were normal and all antibiotics were stopped immediately after the spinal fluid cultures were reported as negative. He was also given 100 mg of thiamine intravenously and started on oral thiamine supplementation of 100 mg daily. Within 24 hours the patient improved dramatically. He became alert and fully oriented. The ophthalmoplegia and vertical nystagmus resolved and the leg weakness improved markedly, with some residual ataxia. The patient was discharged home with continued outpatient physiotherapy.

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Discussion

Wernicke's encephalopathy is a common but preventable disorder due to thiamine deficiency. Alcoholics account for most cases, but thiamine deficiency may infrequently occur in patients with hyperemesis, starvation, hemodialysis (5), cancer, acquired immune deficiency syndrome (AIDS), magnesium depletion (6), gastroplasty/gastric bypass surgery (7), rapid weight loss (8, 9), anorexia nervosa, refeeding syndrome and prolonged intravenous feeding (8, 10). Body stores of thiamine are only sufficient for up to 18 days (11). Thus, depletion can occur rapidly with restricted intake or prolonged vomiting. The Canadian recommendation for thiamine intake is 1.1 mg per day, whereas the American recommendation is 1.4 mg per day (1, 11, 12).

Thiamine is a co-factor of several enzymes, including transketolase and pyruvate dehydrogenase (13). Activity of the latter enzyme, a rate-limiting tricarboxylic acid cycle enzyme, is significantly reduced in autopsied brain tissue of Wernicke's encephalopathy patients and from rats treated with a central thiamine antagonist, pyrimethamine (13). In animal studies, evidence suggests that such enzyme deficits result in focal lactic acidosis, cerebral energy impairment and depolarization of neurons resulting from increased glutamate in vulnerable brain structures. This depolarization may result in n-methyl-d-aspartate receptor-mediated excitotoxicity as well as increased expression of immediate early genes such as *c-fos* and *c-jun*, resulting in apoptotic cell death (13). Another mechanism may involve free radicals and alterations of the blood-brain barrier (13).

Anatomical abnormalities in WE occur mainly in periventricular regions of the diencephalon, midbrain, brainstem and superior vermis of the cerebellum. In acute cases of WE, the lesions consist of symmetrical discoloration with petechial hemorrhages (4). Amnesia is related to lesions of the medial dorsal nuclei of the thalamus. Shrinkage of the mamillary bodies can also be seen (14).

Symptoms and signs indicative of WE usually include vomiting, nystagmus (horizontal more than vertical), medial and lateral rectus muscle palsies leading to unilateral or bilateral ophthalmoplegia, fever, ataxia and progressive mental deterioration that evolves to a global confusional state, coma, and death. Other manifestations of a nutritional deficiency, such as polyneuropathy, may also occur. Tachycardia and orthostasis may be related to an impaired autonomic nervous system or coexistent cardiovascular beriberi. The true prevalence of WE at autopsy is about 3% (3, 4, 15), much higher than what is diagnosed clinically in the general population (0.06–0.13%). Acute WE should be suspected in all alcoholics with neurological symptoms, especially those with evidence of calorie or protein malnutrition and peripheral neuropathy (16). The classic triad of oculomotor abnormalities, gait disturbance and global confusional state occurs only in one-third of the patients. The diagnosis of WE is based on the clinical suspicion and rapid reversal of symptoms after the administration of thiamine. Decreased serum activity of erythrocyte transketolase and MRI (sensitivity 53% and specificity 93%) may be helpful in confirming the clinical diagnosis (16). Typically, there is an increased T_2 signal of the paraventricular region of the thalamus and peri-aqueductal regions of the midbrain. There can also be enhanced T_1 weighted spin-echo (SE) sequences after intravenous gadolinium administration in the acute phase of WE (17). Normal MRI does not exclude the diagnosis of WE. On the other hand, the sensitivity of the CT scan in detecting the characteristic lesion of WE is extremely low (13%), so it is not useful in the diagnosis of this entity (16).

WE is a medical emergency and requires the immediate administration of thiamine in a dose of 50–100 mg, either intravenously or intramuscularly. Doses should be given daily, to build up the body reserves until the patient is able to resume a normal diet. The central nervous system is almost entirely dependent on glucose for its energy requirements. Thiamine is an important co-factor needed in several steps of glucose utilization. Therefore, loading of glucose in a thiamine-deficient person can precipitate a neurological crisis (WE) or can cause rapid worsening of mild symptoms. To avoid this complication, thiamine should always be given prior to any intravenous glucose administration whenever this diagnosis is suspected (18). Patients who recover show improvement of oculomotor palsies within hours of thiamine administration. Ataxia improves more slowly. About one-half the patients recover incompletely and are left with a slow, shuffling wide-based gait and inability to take one step in quick succession after the other. Apathy, drowsiness and confusion diminish gradually. As these symptoms recede, an amnesic state with impairment in recent memory and learning may become more apparent in some cases (Korsakoff's psychosis).

Summary

WE is uncommon in non-alcoholics, but not rare. One should have a high index of suspicion in patients with hyperemesis, starvation, dialysis, cancer, magnesium depletion, AIDS, gastroplasty/gastric bypass surgery, rapid weight loss, anorexia nervosa, refeeding syndrome or prolonged intravenous feeding. Our patient had none of the aforementioned conditions. The recommended treatment is the administration of thiamine, and most patients respond within 24–36 hours.

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Assisted Reproduction:

A Jewish Perspective

Fred Rosner, M.D.

Abstract

Judaism values medicine as a noble profession. Physicians are mandated by the Bible to heal, and those who are ill are obligated to seek healing from their physicians. In Jewish thought, infertility is considered an illness. Hence, in spite of many Jewish legal and ethical questions, assisted reproductive techniques such as artificial insemination, *in vitro* fertilization and surrogate motherhood, within certain limited circumstances, are viewed with favor by most current rabbinic authorities, provided the couple is unable to have a child in the normal manner and after standard medical or surgical interventions have failed.

Key Words: Assisted reproduction, artificial insemination, *in vitro* fertilization, surrogate motherhood.

Introduction

On July 25, 1978, the research efforts of British doctors Patrick C. Steptoe and Robert G. Edwards culminated in the birth of Louise Brown. Steptoe and Edwards had introduced the technique of *in vitro* fertilization and re-implantation of the human embryo into the mother's womb (1). Two years later, the same investigators reported the birth of a boy by the same technique (2). Since then, tens of thousands of healthy babies have been born by this and even newer methods of assisted reproduction.

A woman becomes a "host" or "surrogate" mother when an ovum derived from another woman is fertilized and then implanted into her womb. This now-pregnant woman is the biological, but not the genetic mother. Not surprisingly, *in vitro* fertilization and re-implantation of the human zygote into the womb of either a genetic mother or a surrogate mother raises numerous legal, moral, social and religious questions (3, 4). This essay focuses on some of the Jewish issues and questions related to artificial insemination, *in vitro* fertilization and surrogate motherhood.

Ethical and Moral Concerns

There is no ethical difference between *in vitro* fertilization using the sperm of a man and the egg of his wife, and artificial insemination involving only a husband and his wife. The main ethical questions relate to the use of donor eggs or donor sperm for *in vitro* fertilization, and the use of a surrogate mother as a womb donor. These interventions in the procreation process are becoming more frequent, more complex and more highly technological, thus altering people's understanding of the meaning of "procreation," "family" and "parenthood." The initial ethical question related to assisted reproductive technologies is whether they ought to be used at all (5). The separation of procreation from physical lovemaking is objectionable in Catholic teaching. Judaism and other religions, however, accept assisted reproduction as part of God's mandate to procreate (see below).

Americans cherish their rights of individual choice, liberty and autonomy. These values, however, may conflict with family and community values. People with autonomy are members of communities, and it may therefore be morally legitimate to limit individual choice about assisted reproduction. Critics argue that the introduction of a third party (i.e., a surrogate mother) interferes with the marriage covenant between husband and wife, thereby threatening the traditional societal value of the nuclear family. On the other hand, some people in our modern society condone the use of these new methods of reproduction by single people, and even by homosexual couples (5).

Another ethical concern is that of treating human reproduction as if it were a commodity. Altruism may be replaced by commercialism if women are paid to be egg donors or surrogate

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mothers. Limited access to assisted reproductive technologies by the poor and underprivileged is yet another ethical issue.

The legal and regulatory issues surrounding reproductive technologies concern the ability of government to ban or restrict noncoital reproduction because these technologies may harm embryos, children, consumers or public morals. In the United States, such regulation is a function of state legislatures and review by the courts. However, federal constitutional law significantly limits interference with individuals' exercise of their procreative choices (6).

Ethical and social reasons to oppose surrogacy arrangements include the commercialization of procreation; the destruction of the natural biological and psychological bonds between a woman and her fetus; the use of another woman's body; the loss of the marital bonds created by parenthood, birth and childbearing; and the "cheapening" of human life by the mechanized use of scientific technologies devoid of the love, devotion and intimacy of two happily married people created in the image of God.

Years of debate in scholarly and professional journals and books have failed to resolve these moral and ethical questions. *In vitro* fertilization is strongly opposed by some critics on moral grounds (7), and just as strongly justified by others, who argue that the procedure does not pose any moral problem (8). Despite certain moral objections to the use of the new reproductive technologies, some medical associations endorse these procedures. The American Medical Association has promulgated ethical guidelines for the use of artificial insemination, *in vitro* fertilization, frozen pre-embryos, pre-embryo splitting, surrogate motherhood and related reproductive techniques (9). These guidelines include the obtaining of informed consent (preferably written) after a full explanation and discussion of the proposed treatment, possible side effects, and any alternatives (e.g., adoption).

Judaism and the New Reproductive Technologies

General Principles

The biblical commandment, *be fruitful and multiply,* as decreed first to Adam and Eve (Genesis 1:28) and later to Noah and his sons (Genesis 9:1 and 7) and to Jacob (Genesis 35:11), is discussed in the Talmud (Tractate Yevamot 63b). This biblical statement is at once both a blessing and a commandment. A man is obligated to propagate the race and to sire at least one boy and one girl (Genesis 1:27 and 5:2). The use of assisted reproduction to enable a couple to have children and fulfill the commandment is therefore permissible in Judaism. Non-procreative intercourse, such as occurs if the wife is pregnant or postmenopausal or has had a hysterectomy, is also required, to satisfy the wife's conjugal rights (Exodus 21:10). Physical relations actually serve several purposes in Judaism: procreation, fulfilling the wife's desires, physical release of the husband's sexual pressures, and the maintenance of marital harmony and domestic peace (10, 11).

A cardinal principle in Judaism is that each moment of life is of infinite value. In Jewish law, all biblical and rabbinical commandments are set aside for the overriding consideration of saving a life. It is, therefore, permitted and even mandated to violate the Sabbath to save the life of someone who might not otherwise recover from illness (including mental illness) and/or trauma, or to treat someone who is dying

Another fundamental principle of Judaism concerns the sanctity of human life. Man was created in the image of God. Hence, human beings are holy and must be treated with dignity and respect, both in life and after death. Our bodies are God-given, and we are commanded to care for our physical and mental well being, and to preserve and hallow our health and our lives. Only God gives and takes away life. Are we tampering with the Divine plan for humanity when we perform *in vitro* fertilization and embryo re-implantation?

Since Judaism considers infertility an illness, assisted reproductive technologies may be used to "heal" that illness. Judaism allows, but does not mandate, these techniques for the fulfillment of the precept of procreation. The commandment *be fruitful and multiply* requires only conventional sexual activity within the context of a marital relationship. As long as the methods employed in assisted reproduction do not violate any Jewish legal concerns, such methods are discretionary and permissible (12). Some rabbis frown upon these technologies, because they transform the creation of a human being from a holy act of mutual feeling between husband and wife into a laboratory procedure devoid of the human dimension. The physical union of husband and wife is replaced by a laboratory environment. Lord Immanuel Jakobovits, widely recognized as the "father" of modern Jewish medical ethics, in his classic work on the subject (13), expresses concern about "assessing human beings by their potential value as tool-parts, sperm donors or living incubators, and . . . replacing the . . . human personality [with] test-tubes, syringes and the soulless artificiality of computerized numbers. Man, as the delicately balanced fusion of body, mind and soul, can never be the mere product of laboratory conditions and scientific ingenuity. To fulfill his destiny as a creative [being] in the image of his Creator, he must be generated and reared out of the intimate love joining husband and wife together, out of identifiable parents who care for the development of their offspring, and out of a home which provides affectionate warmth and compassion."

Despite these concerns, a majority of contemporary rabbis rule that it is permissible (but not obligatory) for physicians to offer assisted procreative technologies as a medical treatment for infertility (14). Helping couples to fulfill an explicit biblical commandment — and cure an illness — is thus given high priority.

Artificial Insemination

There is a considerable body of rabbinic writings devoted to artificial insemination (15). They discuss a number of Jewish moral and legal issues: the legal relationship of the offspring to the sperm donor; the possible fulfillment of the commandment of procreation by the sperm donor; the legality in Judaism of procurement of sperm from the husband for artificial insemination and the preferred methods for its procurement; the insemination of the husband's sperm into his wife during or shortly after her menstrual cycle, when she is *niddah* (ritually unclean); the possibility of the insemination itself rendering her ritually unclean by "opening the mouth of the womb"; the question of the woman becoming ritually unclean following birth after artificial insemination; whether a male child conceived in this manner may be circumcised on the Sabbath; whether or not a woman who is inseminated with donor sperm becomes prohibited to her husband; the legitimacy or bastardy of the offspring of artificial insemination using donor sperm; the case where sperm of the husband is mixed with donor sperm prior to insemination; whether or not a husband can divorce his wife if she has undergone artificial insemination without his knowledge; the obligation in Judaism of the father to support his child born after artificial insemination; the status of the child if the sperm donor was a bastard; the case of insemination of semen from a man of priestly descent (a *cohen*) into an adulterous woman; and the possible legality of using sperm from a Gentile donor for artificial insemination into a Jewish woman (16). These questions are discussed and debated by modern rabbinic authorities, based on their understanding of classical Jewish sources.

One of the major sources which the modern rabbis cite is the talmudic discussion (Chagigah 14b) about a virgin who became pregnant in a bathhouse by the accidental insemination of the sperm of a man who had previously discharged semen there. This passage indicates that procreation *sine concubito* was recognized by the talmudic sages. Rabbi Judah Rozanes of Constantinople, the renowned commentator on Maimonides' code of Jewish law, the *Mishneh Torah*, expresses doubt that impregnation through bathing in water into which a man had previously discharged semen can occur (17). However, many authorities, including Rabbi Chaim Joseph David Azulai, Rabbi Jonathan Eybeschutz, and Rabbi Jacob Ettlinger, differ with him and interpret the talmudic passage literally (18).

The second major ancient source indicating the possibility of pregnancy without sexual intercourse is the *Hagahot Smak* (19), by thirteenth century Rabbi Peretz ben Elijah of Corbeil. He describes the possibility of impregnation of a woman who lies on the bed upon which a man other than her husband had slept and had ejaculated on the bed sheets. Several things emerge from Rabbi Peretz's statement. First, generation *sine concubito* was recognized. Second, the offspring is considered legitimate. Third, no prohibition is mentioned concerning cohabitation of the woman with her husband afterwards, even if she has become pregnant from the other man's semen. The only reason for her to avoid contact with the linen upon which another man had lain is to prevent the possibility of incest at a later date, i.e., the child marrying its own sibling. Finally, only prohibited intercourse would make her forbidden to her husband, irrespective of whether or not her male partner had emitted sperm into her genital tract during the prohibited sexual act.

Based on these and other early sources, the modern rabbinic debate can be summarized as follows: Most twentieth-century rabbis rule that artificial insemination using normal semen from the husband is preferred if there is no other way that the wife can become pregnant. Artificial insemination using the semen of a donor other than the husband is frowned upon by most rabbis for a variety of reasons, including the possibility of incest (the child born of such insemination may later marry a sibling, unknowingly), the lack of genealogy (the father's identity is unknown), and problems of inheritance (does the child inherit from the genetic father, the legal father, or both?). A few rabbis (Rabbis Judah Leib Zirelson, Abraham Lurie, Ovadya Hedaya and Eliezer Waldenberg) regard such insemination as adultery, requiring the husband to divorce his wife and the wife to forfeit the marriage settlement (*ketubah*). More authorities, however (Rabbis Ben Zion Uziel, Moshe Feinstein, Sholom Schwadron, Yehoshua Baumol and Aaron Wolkin), state that if no sexual act is involved, the woman is not guilty of adultery and is not prohibited from cohabiting with her husband (10–16).

Regarding the status of the child, rabbinic opinion is divided. Most consider the offspring to be legitimate, as in the case of Ben Sira, the product of conception *sine concubito*. According to homiletical sources, Ben Sira was born to the daughter of the prophet Jeremiah, following impregnation in a bathhouse, in a case similar to that of the virgin described above. A small minority of rabbis (Rabbis Zirelson, Lurie, Hedaya and Breisch) consider the child illegitimate, and at least one rabbi (Waldenberg) considers the child to be a "possible bastard." Many rabbis (10–16) regard the child (legitimate or illegitimate) to be the offspring of the sperm donor in all respects (i.e., inheritance, support, custody, incest, levirate marriage, and the like). Some regard the child to be the donor's offspring only for some legal aspects, but not for others. Some rabbis state that although the child is considered the donor's offspring in all respects, the donor has not fulfilled the commandment of procreation. A minority of rabbinic authorities assert that the child is not considered the donor's offspring at all (10–16).

Most rabbis allow the husband to provide semen both for analysis and for insemination, but a difference of opinion exists as to the method to be used in its procurement. Masturbation should be avoided if at all possible; *coitus interruptus*, retrieval of semen from the vagina, or the use of a condom (assuming it has no spermicide) seem to be the preferred methods.

In Vitro Fertilization

The use of a man's sperm and his wife's eggs for *in vitro* fertilization and re-implantation into the wife's womb, as in the Louise Brown case, is permitted. The rabbinic reasoning is that there is no question of adultery involved, since the sperm used is that of the husband. Sperm and egg procurement for this procedure are permissible, based on a talmudic passage (Yevamot 76a), because the aim is to fulfill the biblical commandment of procreation. The offspring is legitimate and the parents thereby fulfill their obligation to have children. Most twentieth-century rabbis, including Rabbis Auerbach, Baumohl, Frank, Feinstein, Mintzberg, Schwadron, Shapiro, Waldenberg and Wolkin, support this view (11).

However, certain serious moral and Jewish legal problems arise if one uses sperm other than that of the husband. These objections have been discussed above. Furthermore, if one obtains several eggs from the mother's ovary at the same time and fertilizes them all, so as to select one or more for re-implantation, is one permitted to destroy the other fertilized eggs? Do they not constitute human seed, which is not to be "cast away for naught"? Is one permitted to perform medical research on the unused fertilized eggs? Is the destruction of such fertilized ova tantamount to abortion? Is such a fertilized ovum regarded as "mere water" during the first forty days of its development? The generally accepted Judaic view is that a fertilized egg does not attain human status until it is implanted in the woman's womb. Hence, excess fertilized eggs may be frozen for later use, discarded, or used for the advancement of scientific knowledge (11, 12, 20). Some rabbis prohibit the use of donor eggs for *in vitro* fertilization primarily because of concern about "chaos in the world," that is, confusion about one's relatives and the remote possibility of a brother-sister marriage years later (12, 21).

Surrogate Motherhood

For a woman who is unable to carry a pregnancy to term, the permissibility of resorting to host motherhood poses serious questions in Jewish law (10–16). The foremost question is whether the would-be egg donor, i.e., the woman in whom a pregnancy is contraindicated or not anatomically possible, can agree to *in vitro* fertilization of her ova prior to their implantation into a host. The related question is whether the intended host is allowed to undergo an implantation procedure. Questions analogous to those in artificial insemination arise, as discussed above.

Maternal identity in situations involving a host mother is discussed in great detail by noted Jewish bioethicist Rabbi J. David Bleich (21), who concludes that "the consensus of rabbinic opinion is that a maternal-filial relationship is generated between the gestational mother and the child despite the absence of any genetic relationship, by virtue of parturition alone." The possibility that Jewish law may recognize the existence of a maternal relationship between the genetic mother, i.e., egg donor, and the child, cannot be excluded even if that child was born to a surrogate mother.

Other Jewish legal questions in regard to the identity of the mother include the following: Assuming the paternity to be different, are children conceived *in vivo* related to a child born to their mother when she serves as a surrogate? Are these children prohibited from marrying that child? What is the Jewish law if the egg donor is not Jewish, and the surrogate or host woman is Jewish? What about the situation in which the egg donor is Jewish, but the host mother is not? Bleich (21) rules that in this situation, the child requires conversion. What happens if the host woman was not Jewish when the fertilized ovum was implanted into her womb, but converted to Judaism during the pregnancy — is the child required to undergo conversion? If a surrogate mother gives birth to a boy, does he, if he is a firstborn, undergo redemption of the firstborn?

Conclusion

Technical advances in the area of *in vitro* fertilization and surrogate motherhood have resulted in significant changes in the concepts of fertility, parenthood, and family identity. Many advances in reproductive technology have brought great hope to infertile men and women. It is thus an important medical approach to a serious problem. Ethical and legal issues arising from this technology have been considered in detail and depth by modern rabbinical authorities.

The Talmud states that there are three partners in the creation of a human being: the Holy One, blessed be He, the father, and the mother. (Niddah 31a). Some physicians can now serve as a fourth partner, facilitating these three in the siring of children by assisted reproduction.

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The White Coat Ceremony

RUTH M. ROTHSTEIN

I HAVE SPOKEN TO A NUMBER OF DOCTORS about the meaning of the white coat ceremony, and all of them spoke with enthusiasm about what it meant for them, how excited they were, and that it was truly the beginning of their life as a doctor. The essential aim of the white coat ceremony is to underscore the need for personal duty and professionalism to accompany high academic standards, as medical students learn to become physicians. The ceremony attempts to codify the core values of altruism, duty and compassion that doctors must acquire and exhibit. The coat symbolizes the need for physicians to possess not only the knowledge and skills required to care for patients, but also the empathy and compassion to treat them as human beings.

Over the past few decades, during which we have witnessed a tremendous explosion of scientific information and technology, we have also seen a surge in the use of alternative medicines such as herbal therapy, acupuncture and massage therapy, in response to public demand and need. Medical schools are responding to this demand by introducing their students to these alternative treatment methods. For example, at one medical school, future doctors learn about the religious and spiritual aspects of illness and healing from chaplains.

At the University of Illinois in Chicago, second-year students take a course in managing HIV/AIDS patients with alternative medicines. Today, East is meeting West at the doctor's office. This new wave, called integrated medicine, is the practice of using biology-based treatments that rely on scientific research and alternative medicine together.

Two years ago, Cook County Hospital and Rush-Presbyterian-St. Luke's Medical Center opened a 760,000 square foot infectious disease facility that, at the urging of the community, integrated massage therapy, reflexology and stress reduction into the daily regimen of medical treatments provided to patients. For the physician, it means treating the whole person rather than the disease, a concept that is both exciting and important for every future doctor to embrace. Stated another way, every physician-to-be must avoid the pitfall of practicing medicine without a heart and a soul.

The Symbolism of the White Coat

White was chosen with good reason as a symbol of the medical profession. It has very positive connotations. Traditionally, in Western culture, whiteness has symbolized such positive values as life, purity, innocence, and goodness. In medical terms it could be said to symbolize cleanliness, honor and selflessness. But, as Delese Wear, a professor of medical humanities, has pointed out, there is also a darker symbolism hidden behind the altruism, compassion and excellence (1): "Wearing the white coat . . . may actually promote an effect which is opposite of that which the coat is meant to symbolize." The white coat should never become a symbol of hierarchy, status, power, and negative separation. Doctors must not "become" the coat. They must never be insensitive to the way their patients respond to them. They must always remember that good medicine is predicated on mutual respect, honest communication, and shared humanity.

The Oath

At the conclusion of the white coat ceremony, doctors-in-training recite an oath modeled in part on the Hippocratic Oath. By taking this oath, they become part of a 2000-year-old tradition of ethical and moral obligation.

Essentially, they are pledging, in the presence of their professors, colleagues, families and friends, that in all the years ahead, they will dedicate their lives and their talents to the alleviation of human suffering, and provide the highest level and quality of service to their community and to society. In short, the white coat ceremony reaffirms the very reasons why one wants to be a physician in the first place.

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The following remarks were originally delivered to the Mount Sinai School of Medicine, New York, NY, Class of 2004 on the occasion of the White Coat Ceremony, September 13, 2000. They have been edited for publication.

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Key Words: White Coat Ceremony.

Working with the Community

Let me offer some personal reflections stemming from 40-plus years of attempting to provide health care in the inner-city of Chicago — as president and CEO of Mount Sinai Hospital in Chicago, as director of Cook County Hospital, and today as chief of the third largest public health system in the country, the Cook County Bureau of Health Services.

At Mount Sinai of Chicago, there was a lack of understanding between the hospital personnel, the board of trustees and the community. The area surrounding the hospital, which had formerly been all Jewish, had changed. As the Jewish population moved away, African-Americans and Latinos replaced them.

Instead of getting to know the new residents of the community and determining what their health care needs might be, the hospital built a wall around itself, closing itself off. It took a lot of hard work on the part of many people to tear down those walls and build up a new spirit of cooperation and mutual trust and respect, a spirit of compassion and caring that still exists at Mount Sinai today.

What we learned, above all, is that health care is about empowering, involving and transforming communities. It is about caring for the health of all the people. It is about working for economic security, as well as delivering quality medical service. It is about creating an environment that fosters strong partnerships and mutual respect and cooperation among physicians, medical institutions and the people they both serve.

Cook County Bureau of Health Services

When I left the private sector for the public sector, I found a larger version of these same problems. The six different institutions that make up our bureau had different and sometimes conflicting missions. There was little coordination of services. There was little effort to form partnerships between the institutions. One of my priorities was to begin a dialogue among all the bureau's member institutions — to open new channels of communication. Through these channels, we sought to identify the many social and economic factors that impact the health status of the people within the communities we serve. We also developed partnerships with private sector providers, so that we could cooperate in using resources and improving access to health care.

Keep in mind that, not only are the vast majority of the patients at Cook County's health care institutions underserved, but also 80 percent of all the outpatients who come to Cook County are uninsured. Many new members of the medical profession will be working in such an environment. I hope you will. But regardless of the population you serve, it is imperative that you give them your best.

Conclusion: A Series of Challenges

Tomorrow or the next day, you will be immersing yourselves in your studies, at a level of intensity that you have never experienced before in your life. Regardless of the difficulty, I am confident that you will master your material. But before you lose sight of this day and this important ceremony, let me offer you some different challenges.

- I challenge you to go outside the walls of the academic health center and into the community, to provide the service of your hands, your heads and, most of all, your hearts, to the uninsured, the underserved, the disenfranchised — the forgotten souls outside the system.
- In the same vein, I challenge you to be politically active — to take a stand against the inequities that permeate all aspects of the health care system and to take a stand on behalf of the 45 million uninsured Americans, by advocating that health care is a right, not a privilege.
- I challenge you to ask your professors and your mentors to share with you their personal struggles to maintain a balance between medicine as a career and their own lives.
- I challenge you to be lifelong learners not only of medical facts and figures, but also of all sources of wisdom, including the social sciences, the arts and the humanities. The more well-rounded you become, the better doctor you will be.
- I challenge you to embrace the highest moral, ethical and professional values, and never to compromise these beliefs.
- I challenge you to treat everyone you encounter in the practice of your profession — colleagues, nurses, allied health, residents, fellows, students, patients — with respect and dignity.
- Finally, I challenge you — even in a world gone cynical — to serve the rich and the poor, the high and the low, the mighty and the meek — with the flame of mercy and the light of compassion.

Members of the class of 2004, these are your challenges. I hope that you will meet them, for much of our future and the future of health care depend on you. Thank you.

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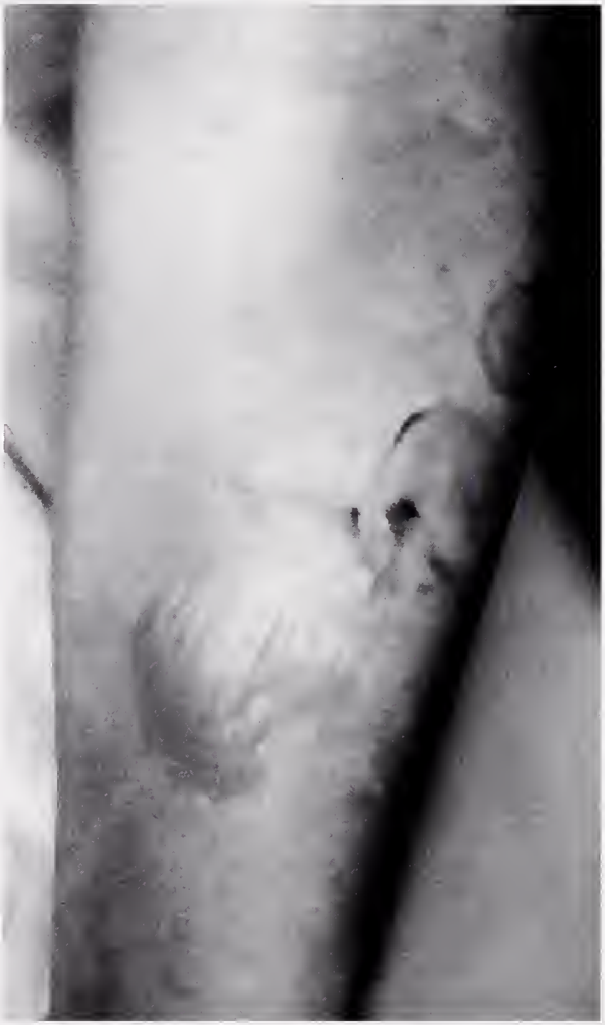
Thermal Burn



BULLOUS LESIONS are characteristic in a second-degree thermal burn.

—Jacob Baral, M.D., and Mark G. Lebwohl, M.D.

Interactions between HIV-Related Medications and Methadone:

An Overview

Marc N. Gourevitch, M.D., M.P.H.

Updated March 2001
Adapted and updated by MN Gourevitch from an article originally published as: Gourevitch MN, Friedland GF. Interactions between methadone and medications used to treat HIV infection: A review. Mt Sinai J Med 2000; 67:429–436.

TABLE

Medication	Formally Studied?	Effect on Methadone	Effect on HIV-Related Medication	Reference
NRTI				
Zidovudine (AZT)	Yes	None	↑ AZT AUC by 40%	(1, 2)
Didanosine (ddI)	Yes	None	↓ ddI AUC by 60%	(3)
Zalcitabine (ddC)	No	Not studied or reported	Not studied or reported	
Stavudine (d4T)	Yes	None	↓ d4T AUC by 18%	(3)
Lamivudine (3TC)	Yes	None	Not studied	(4)
Abacavir (ABC)	Yes	↑ Methadone clearance	↑ Time to peak concentration ↓ Peak concentration	(5)
NNRTI				
Nevirapine	Yes	Withdrawal symptoms ↓ Methadone levels by 46% Need for ↑ methadone dose observed	Not studied or reported	(6–8)
Delavirdine	No	↑ Methadone levels predicted	Not studied or reported	
Efavirenz	Yes	↓ Methadone levels by 48% Heroin use relapse Need for ↑ methadone dose observed	Not studied or reported	(8, 9)
PI				
Indinavir	No	Not reported	Not reported	
Ritonavir	Yes	↓ Methadone levels reported† ↓ Meperidine levels	No effect reported †	(10) (11)
Nelfinavir	Yes	↓ Methadone levels, but no withdrawal symptoms observed	No	(12)
Saquinavir	Planned	Not studied or reported	Not studied or reported	
Amprenavir*	Yes	↓ Methadone levels, but no withdrawal symptoms observed	Not studied or reported	(13)
Lopinavir*	PDR data only	↓ Methadone levels reported†	Not studied or reported	(14)
Other medications used in the treatment of HIV-infected persons				
Rifampin	Yes	↓ Methadone levels, often sharply	None reported	(15)
Rifabutin	Yes	No change in methadone levels Mild narcotic withdrawal symptoms	None reported	(16)
Fluconazole	Yes	↑ Methadone levels by approximately 30%, clinical significance unknown	None reported	(17)
Phenytoin	Yes	↓ Methadone levels, often sharply	None reported	(18)
Phenobarbital	Yes	↓ Methadone levels, often sharply	None reported	(19)
Carbamezipine	Yes	↓ Methadone levels	None reported	(20)
Fluvoxamine*	No (case series only)	↓ Methadone levels by 20–100%	None reported	(21, 22)
Fluoxetine*	No (case series only)	Minimal ↑ methadone levels	None reported	
Sertraline*	Yes	Transient mild ↑ methadone levels	None reported	(23)

NRTI = nucleoside reverse transcriptase inhibitors
NNRTI = non-nucleoside reverse transcriptase inhibitors
PI = protease inhibitor
AUC = area under curve
† Study design limits clinical utility of results.
* New

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DERMATOLOGY

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Introduction

Mark Lebwohl, M.D.

Mount Sinai's important contributions to the field of dermatology stem from the work of numerous researchers and clinicians, some of whom were not even dermatologists. For example, the original description of the spots which came to be recognized as a diagnostic sign of measles (Koplik's spots) was made by Dr. Henry Koplik, a Mount Sinai pediatrician (1). The original description of collagen vascular disease was made by Paul Klemperer, then chairman of pathology at Mount Sinai.

The beginnings of the Department of Dermatology can be traced to a clinic for skin and venereal disease founded in 1891 in Mount Sinai's Out-Patient Department. In 1893, Dr. Sigismund Lustgarten was appointed consulting dermatologist. Seven years later, he became attending dermatologist, the equivalent of chief of service.

With the death of Dr. Lustgarten in 1910, Dr. Herman Goldenberg became attending physician. His eminence in the treatment of syphilis was widely acknowledged; he became the first clinician to receive an allotment of the arsenical compound Salversan when it became available for general distribution.

In 1929, Drs. Walter Highman and Isadore Rosen were named attending dermatologists, and syphilis continued to be a major focus of research and treatment. In 1940, a major breakthrough was announced in an unusual press conference highlighting the discovery of the 5-day drip therapy for syphilis that had been devised by Drs. Louis Chargin, Harold T. Hyman and William Leifer. This pioneering treatment radically cut the time and cost of treatment, but was shortly to be eclipsed by the development of penicillin.

In 1946, Dr. Samuel Peck became chief of Dermatology and established a residency program that graduated its first doctor in 1948. Peck was renowned for his pioneering studies in contact dermatitis, his research on the first topical antifungal agent, undecylenic acid, and his work on occupationally induced hyperpigmentation. He presented the opening paper at the first meeting of the Society for Investigative Dermatology.

At Peck's retirement in 1971, Dr. Arthur Glick was named acting chairman. He authored papers on industrial dermatoses and expanded the dermatologic surgery clinic. In 1975, Glick retired and Dr. Harry Shatin became the first full-time chairman of the department. A superb clinician, he emphasized teaching residents and providing optimal patient care. He himself was a noted venereologist.

With the appointment in 1979 of Dr. Raul Fleischmajer as chairman, the department expanded its research activities. Fleischmajer brought clinical and scientific expertise to the field of scleroderma and the basic science of collagen. Recently, the current assistant chairperson, Dr. Marsha Gordon, made an important contribution on a related disease, when she discovered that patients diagnosed with eosinophilic fasciitis had ingested L-tryptophan, an observation that coincided with the description of the eosinophilia-myalgia syndrome (2). Several years earlier, Dr. Poliak and her associates (3) were the first to describe reactive perforating collagenosis associated with renal disease and diabetes. These observations have been repeated by many and are the basis for the classification of the so-called perforating disorders associated with renal failure.

Scientists in our department have contributed greatly to an understanding of pseudoxanthoma elasticum (PXE). The diagnosis of this disorder by scar biopsy led to the observation that patients with accelerated cardiovascular disease can have occult PXE (4, 5). Members of our department also reported the association between PXE and cardiac valvular abnormalities (6). A study of the connective tissue matrix in patients with PXE was conducted by members of our department, who reported their observations of dramatic abnormalities in glycosaminoglycans (7). In addition, our department has played a major role in the localization of the genetic defect in PXE and in the identification of the abnormal gene.

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Key Words: Dermatology department, Mount Sinai School of Medicine, history

Dermatopharmacology is another area in which Mount Sinai's Dermatology Department has pioneered. We were the first to report an interaction between ultraviolet light and calcipotriene, a vitamin D derivative used topically in the treatment of psoriasis (8). We have also studied interactions between various topical medications applied simultaneously on the skin, and have noted clinically significant effects with drugs such as topical corticosteroids, salicylic acid, calcipotriene, and tazarotene. The photosensitizing potential of tazarotene was first observed by members of our department.

Dr. Huachen Wei, director of our department's laboratories, brought expertise in cutaneous carcinogenesis and its prevention by a new agent, genistein, derived from the soy bean. Dr. Wei is a pioneer in the study and application of genistein and its effects. He has demonstrated that topical or oral genistein prevents chemically induced skin cancers and those induced by ultraviolet light (9), and has shown that photoaging and sunburn can be prevented by genistein.

This dermatology theme issue of *The Mount Sinai Journal of Medicine* draws on many of the strengths of the Dermatology Department. Dr. Douglas Altchek, the department's historian and a capable clinician, has contributed an article on the history of dermatologic instrumentation. The chapter on treatment of pemphigus was authored by Dr. Michael Fellner, an internationally recognized authority on this disease, and Dr. Allen Sapadin, one of our brightest and most productive recent graduates. Dr. Ron Shelton, a Mohs' surgeon on our voluntary faculty, has written a valuable chapter on the recognition and treatment of skin cancers. Dr. Susan Bershad, drawing on her background in nutrition, ran an extremely important clinical study examining retinoid-induced hyperlipidemia (10) at Mount Sinai. She has written a therapeutic update on the subject of acne vulgaris for this issue. Dr. Bershad is the originator of short contact tazarotene therapy. Dr. Robert Phelps, head of dermatopathology at Mount Sinai, has submitted an update on his previous discussion of the diagnosis of panniculitis (11). Dr. Nelson Novick, one of the department's most prolific writers, has contributed a case report and literature review on an important subject, namely, unilateral chronic dermatitis of the nipple. Dr. Raul Fleischmajer, chairman emeritus of the department and an authority on the pathophysiology of sclerodermatous skin disorders, co-authored a chapter on that subject with Dr. Allen Sapadin. Drs. Donald Rudikoff and Joel Gelfand, co-authors of a landmark paper demonstrating the safety and efficacy of UVB in dermatoses associated with HIV infection (12), joined to contribute a manuscript on pruritic disorders of HIV. John Cunningham, formerly of Mount Sinai's Surgery Department, co-authored an important article on necrotizing fasciitis, and one of our residents, Ronit Hamuy, contributed a case report describing the development of cutaneous polyarteritis nodosa following group A streptococcal necrotizing fasciitis.

Students rotating through our department are encouraged to do research and write scholarly articles, and some of the best of those articles have been incorporated into this issue. Dr. Robert Buka has written a review of longitudinal melanonychia in children. This sometimes ominous physical sign may portend malignant melanoma in certain cases. Amy Krupnick, M.D., co-authored a case report of a patient with congenital combined immunodeficiency who developed a granulomatous disorder suggestive of leprosy. Dr. Elizabeth Goldberg co-authored a case report on zosteriform Darier's disease. Our department also provides clinical dermatology instruction to students at the New York College of Podiatric Medicine. One such student, Dr. Neil Blitz, contributed a state-of-the-art review of pyoderma gangrenosum.

These chapters have been gathered into a single theme issue by two of our most capable clinicians, Drs. Donald Rudikoff and Allen Sapadin, who have previously collaborated on a number of medical papers and posters presented at national meetings. This issue represents only a small sampling of the talent and accomplishments in Dermatology at Mount Sinai.

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Immunopathogenesis of Scleroderma – Evolving Concepts

Allen N. Sapadin, M.D.[1], Adam C. Esser, M.D.[2], and Raul Fleischmajer, M.D.[3]

Abstract

Scleroderma, or systemic sclerosis, is a connective tissue disease which may affect various organ systems including skin, lungs, gastrointestinal tract, cardiovascular system and kidneys. While the etiology is not clear, it is currently believed that scleroderma may represent an autoimmune response to an unknown antigen. In this regard, there is evidence that both humoral and cellular immunity may play roles. The pathophysiology is complex and consists of three major features: (1) vascular damage; (2) mononuclear cellular infiltrates; and (3) massive deposition of newly synthesized connective tissue, mainly collagen. The major pathologic features of scleroderma and the roles of humoral and cellular immunity in its pathogenesis are reviewed and summarized.

Key Words: Scleroderma, systemic sclerosis, adhesion molecules, cytokines.

SCLERODERMA, OR SYSTEMIC SCLEROSIS, is a connective tissue disease which may affect various organ systems (1). While the etiology is not clear, it is currently believed that scleroderma may represent an autoimmune response to an unknown antigen. In this regard there is evidence that both humoral and cellular immunity may play a role. Autoantibodies have been demonstrated in the CREST (calcinosis, Raynaud's disease, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome (anticentromere) and in the diffuse forms (scleroderma-70 and anti-nucleolar antibodies) (2, 3). There is also a possibility that scleroderma may represent an acquired disease secondary to a toxic chemical or an organism. Scleroderma-like syndromes have been reported following: Lyme disease; ingestion of adulterated oil (toxic oil syndrome) and tryptophan; inhalation of polyvinyl chloride; and the use of silicones for cosmetic procedures.

The pathophysiology is complex and consists of three major features: (a) vascular damage; (b) mononuclear cellular infiltrates; and (c) massive deposition of newly synthesized connective tissue, mainly collagen (4). It is very likely that these three events take place simultaneously, and that the ischemia and final fibrosis are responsible for the development of organ insufficiency. There is evidence that blood vessel damage and collagen deposition may be mediated by cytokines released by lymphocytes and monocytes (5). This paper reviews the main pathologic features of scleroderma, and summarizes the roles of humoral and cellular immunity in its pathogenesis.

Vascular Pathology

The vascular hypothesis suggests that the primary event in scleroderma occurs at the level of capillaries and small blood vessels. Blood vessel involvement in many organ systems is well documented (6, 7). The capillary network appears to be greatly diminished, as shown by capillaroscopy (8) and by immunofluorescence studies with laminin and type IV collagen antibodies (9). Electron microscopy showing damaged endothelial cells and reduplication of the basal lamina have verified capillary alterations (10, 11). Small arteries reveal thickening of the media, hyaline or fibrinoid degeneration, intimal thickening, and subintimal deposition of collagen, leading to narrowing of the lumen and ischemic necrosis (6, 7).

A striking feature in scleroderma is destruction of endothelial cells in capillaries (11). Recently, activation of endothelial cells in scleroderma skin has been demonstrated by increased expression of E-selectin (12). E-selectin, an adhesion molecule expressed in activated endothelial cells, is involved in the adhesion of these cells to lymphocytes, monocytes and neutrophils. More recently, it has been shown that

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E-selectin, tumor necrosis factor (TNF-α) and mast cell infiltrates could be noted in salivary glands in early stages of scleroderma where clinical features were restricted to Raynaud's phenomenon and abnormal capillaroscopic findings (13).

Mononuclear Cell Infiltrates

Mononuclear cell infiltration in various organ systems occurs early in the pathophysiology of scleroderma. These infiltrates have been noted in skin (14), smooth muscle (15), esophagus (16) ileum and jejunum (17), synovium (15) and liver (18). In the skin, cellular infiltrates consisting of lymphocytes, plasma cells and fibroblast-histiocytic types were found around small blood vessels, in eccrine sweat glands and in the subcutaneous tissue (14) (Fig. 1). In a study of 65 patients with systemic scleroderma, 49% of the biopsy specimens demonstrated a cellular infiltrate. The distribution of the infiltrate was perivascular in 26% and diffuse in 23% of the patients studied. By contrast, in 43 patients with localized scleroderma, infiltrates were seen in 84% of the patients studied (14). The cells found in the infiltrates fell into three groups: (a) mature lymphocytes, T-lymphocytes, immature plasma cells and plasma cells; (b) fibroblasts, fibrocytes, and fibroblast-like cells; and (c) macrophages, undifferentiated mesenchymal cells and monocytes (19). The high frequency and the severity of these infiltrates, particularly in localized scleroderma, suggest that these infiltrates represent an early stage preceding the development of fibrosis. Subsets of mononuclear cells have been identified in the skin and peripheral blood of patients with systemic sclerosis by means of monoclonal antibodies (20). Almost all the cells in scleroderma skin biopsies are activated T lymphocytes, as evidenced by the expression of HLA class II molecules. While the preponderance of cells in the skin are CD4$^+$ (21), the majority of those in bronchiolar lavage specimens from patients with alveolitis are CD8$^+$ (22). An elevated T-helper/T-suppressor lymphocyte ratio was found in the peripheral blood samples from scleroderma patients. It has been suggested that the antigenic stimulus for the dermal inflammation observed in scleroderma could be the exposure of basement membrane type IV collagen (23).

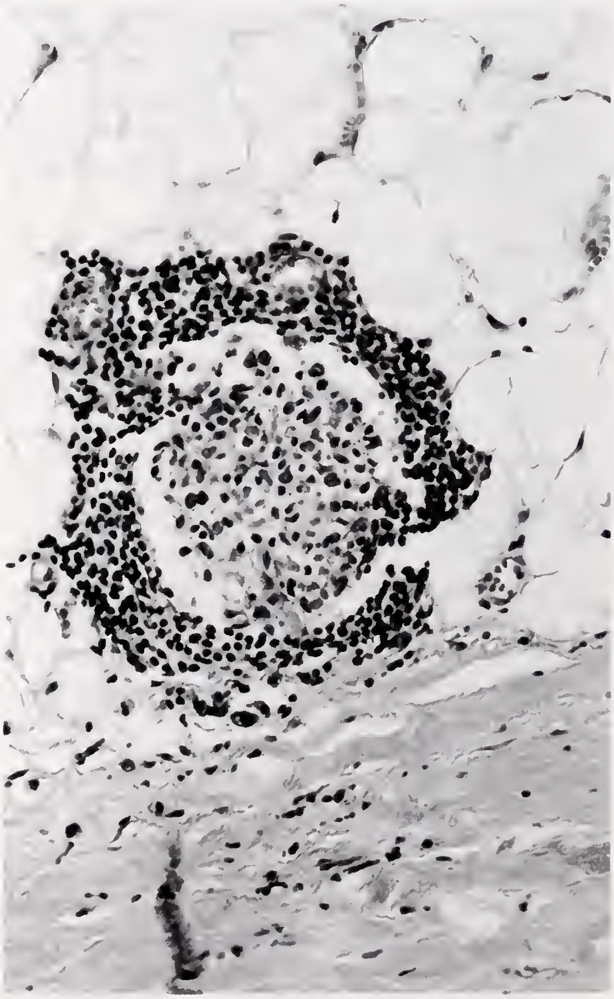

Fig. 1. Systemic scleroderma. Note mononuclear cell infiltrate surrounding a capillary and invading adipose tissue (hematoxylin and eosin; original magnification x 200) (14).

Fibrosis

The most striking feature of scleroderma pathology is the deposition of newly synthesized connective tissue, leading to fibrosis. In the skin, fibrosis involves the dermis and subcutaneous tissue. During the early stage, there is an increase in the fibroblast population. The collagen appears homogeneous and stains lightly with trichrome stains.

In addition, there is deposition of glycosaminoglycans and glycoproteins, as demonstrated by Alcian blue and PAS stains. Early deposition of type III collagen within cellular infiltrates in scleroderma skin has been observed by means of immunofluorescence microscopy (24, 25). This collagen can be stained with silver and probably represents newly synthesized collagen or reticulin fibrils. Types I and III collagen can be demonstrated throughout the dermis and subcutaneous tissue.

The interpretation of the above data may be subject to revision in view of findings suggesting that type I and type III collagen molecules may be hybridized within single collagen fibrils (26, 27). In one study, staining for the aminopropeptide of type I procollagen was noted at the epidermodermal junction (which is normal), around capillaries, and in the lower dermis at the junction of the reticular dermis and subcutaneous tissue (9). Staining for the aminopropeptide of type III procollagen was intense throughout the dermis.

In addition, deposition of fibronectin has been shown in the lower dermis and subcutaneous tissue. It is likely that the focal increase in fibronectin will correspond to areas of active collagen synthesis, since fibronectin is a chemotactic factor for fibroblasts. An increase in fibronectin has also been demonstrated in scleroderma skin and in cultured scleroderma fibroblasts when performing chemical analysis.

Electron microscopy of dermal fibrosis reveals areas consisting of fine collagen fibrils, about 10–30 nm in diameter, embedded in abundant ground substance; areas showing a bimodal distribution of 40 nm and 80 nm collagen fibrils; and areas of tightly packed, thick collagen fibrils about 80–100 nm in diameter (25, 28). Considerable disorganization of collagen bundles is seen throughout the areas of fibrosis. The nature of these fibrils is still not well understood, although it has been suggested that they represent type III collagen or early immature type I collagen. Immunoelectron microscopy has been performed with antibodies directed against the aminopropeptides of type I and type III procollagens. These studies showed that although most thin fibrils retain the aminopropeptide of type III procollagen (pN-collagen), some also label for the aminopropeptide of type I procollagen (29).

Chemical analysis of scleroderma skin by ELISA also revealed a 2.5-fold increase in pN-III collagen and a 3-fold increase in fibronectin, thus corroborating previous immunofluorescence studies. The above data suggest that most thin collagen fibrils in scleroderma skin represent type III collagen, which retains its aminopropeptide. However, this interpretation may be subject to revision in light of recent data showing that collagen fibrils may be hybrids of type I and type III collagens (26, 27). One may speculate that in scleroderma, retention of the aminopropeptide of type III collagen may, by steric hindrance, stop the growth of the fibril. It is noteworthy that pN-type III propeptides have been found to be increased in scleroderma serum and that the increase correlated with fibrotic activity in those patients (30).

Fibroblast Heterogeneity

Scleroderma fibroblasts show an increase in collagen synthesis as compared to normal controls (31); this metabolic change is most striking in those fibroblasts derived from the lower dermis (32, 33). When fibroblasts were cultured from various levels of involved scleroderma skin, considerable metabolic heterogeneity (collagen and fibronectin synthesis) was observed, suggesting the presence of different clones. The highest collagen-producing populations were found at the lower levels of the dermis. Furthermore, several cultures revealed a synchronized increase in type I and type III collagens, and fibronectin (33). Activated fibroblasts in scleroderma skin have been demonstrated by *in-situ* hybridization with α_1(I) collagen cDNA clones. These studies showed that fibroblasts at the lower levels of the dermis and around blood vessels were the most active, again suggesting possible clonal selection (34).

There is considerable doubt that fibroblasts grown in a monolayer (culture) accurately reflect the *in-vivo* situation. To address this issue, *in-situ* hybridization was performed with specific antisense RNAs on frozen sections of skin from patients with localized and systemic scleroderma (34). Enhanced messenger RNA levels for type I and type III collagen were demonstrated, indicating increased transcriptional activity for these collagens in scleroderma fibroblasts (35).

Increased collagen can be due to overproduction or decreased breakdown. Collagenase activity was found to be decreased in scleroderma skin, suggesting a possible reduction in collagen breakdown (36). However, this finding may be secondary to a reduction in the dermal cell population during the fibrotic stage. Furthermore, collagenase activity and collagen degradation were normal in cultures of scleroderma fibroblasts.

The elevated metabolic activity of scleroderma fibroblasts could be attributed to several factors: (1) a defect in the regulation of collagen synthesis; (2) selection of fibroblast clones that express a phenotype for high matrix protein synthesis, and (3) release of cytokines that may activate monocytes-macrophages, T-lymphocytes and platelets.

Immunopathology

The etiology of scleroderma remains unknown, although it has been suggested that it may represent an autoimmune process which involves both humoral and cellular immunomechanisms. Circulating autoantibodies are common in scleroderma, including those against centromere, topoisomerase, nucleolus, and smooth muscle cells. It is uncertain what the role of these antibodies is, since in some patients typical scleroderma without circulating autoantibodies can be seen. Furthermore, there is no strong correlation between autoantibody titers and severity of the disease. Autoantibodies against type I collagen, type IV collagen and laminin have been reported, although these autoantibodies may represent a secondary phenomenon. Moreover, there are no consistent HLA-phenotypes to support an autoimmune process. Perhaps the most convincing evidence for an autoimmune process in scleroderma is its clinical similarity with chronic graft-versus-host disease.

The mononuclear cell infiltrates, perhaps triggered by vascular damage or some unknown antigen, result in the recruitment of lymphocytes (T and B cells), macrophages and fibroblasts. An increase in the T-helper population may explain: (a) the increase in B-cell activity with formation of autoantibodies and (b) an expansion of reactive T-cell clones. These activated T-cell clones may release lymphokines that are chemotactic for fibroblasts. Moreover, they may stimulate fibroblast proliferation as well as collagen and glycosaminoglycan synthesis. Monocytes could also be stimulated to release monokines such as fibronectin and interleukin-1. Fibronectin is chemotactic for fibroblasts, and interleukin-1 may stimulate cell proliferation and increase collagen, collagenase and hyaluronate production by fibroblasts. In addition, specific lymphokines released by T-cells may be responsible for endothelial cell damage.

Humoral Immunity

Autoantibodies can be demonstrated in about 70-95% of patients with systemic sclerosis, provided the proper substrate (Hep-2 cells) is used. These circulating antibodies give different patterns by indirect immunofluorescence microscopy: homogeneous, speckled, centromere distribution and nucleolar. Five types of autoantibodies have been described in systemic sclerosis: anticentromere, scleroderma-70 (Scl-70), nucleolar, anti-Fcγ receptors and antimitochondrial (Table 1).

TABLE 1
Autoantibodies in Scleroderma

Antibody	Clinical Significance
1. Scleroderma-70	diffuse form
2. Anticentromere	CREST
3. Nucleolar	
(a) Fibrillarin	diffuse form
(b) RNA Polymerase	diffuse form
(c) PM-Scl	moderate severity
(d) Th/To	mild form
4. Fcγ-receptor	may be indicator of disease activity
5. Anti-mitochondrial	primary biliary cirrhosis

Anticentromere Autoantibody

This autoantibody is present in 99% of patients with the CREST syndrome. By immunofluorescence microscopy, it gives a discrete speckled pattern (37, 38). The anticentromere autoantibody (ACA) is usually seen in patients with sclerodactyly, without facial involvement or acrosclerosis. However, the ACA has been reported in patients with Sjögren's syndrome and diffuse scleroderma. The ACA has also been reported in 20% of patients with Raynaud's disease; they may eventually develop systemic sclerosis. Interestingly enough, the ACA may also be present in Raynaud's phenomenon associated with rheumatoid arthritis and Hashimoto thyroiditis. Thus, the ACA, while not present in all cases, could also be regarded as a marker for Raynaud's phenomenon. Since the ACA is so frequently associated with CREST, it may predict a good prognosis as it relates to progression of the disease. However, it should be stressed that the CREST syndrome can be associated with two serious complications, namely biliary cirrhosis and pulmonary hypertension.

Scleroderma-70 (Scl-70)

The Scl-70 autoantibody is usually seen in association with diffuse scleroderma. The Scl-70 and ACA autoantibodies are exclusive of each other. The antigen for Scl-70 antibody has been identified as the nuclear enzyme DNA topoisomerase, which regulates chromosomal super-coiling during the cell cycle. The Scl-70 autoantibody demonstrates, by immunofluorescence, a fine speckled pattern with or without nucleolar staining, and is present in 20% of patients with systemic sclerosis. This autoantibody is a marker for systemic sclerosis and is usually seen with diffuse skin involvement, sometimes associated with acroosteolysis and pulmonary hypertension. It has also been observed with idiopathic Raynaud's phenomenon and the CREST syndrome.

Nucleolar Antibodies

Antibodies directed against nucleolar components are present in about 50% of patients with systemic sclerosis. The three major antibodies in this class are U3-RNP, Th/To and PM-Scl. Several antigens have been isolated, including 4-6 S nucleolar RNA, anti-RNA polymerase 1, U3-RNP and nucleolar organizer. The antifibrillarin or U3-RNP antibody is usually associated with severe scleroderma, including diffuse skin involvement, digital infarcts and ulcers, extensive telangiectasias, calcinosis, muscle and small bowel involvement, and pulmonary hypertension. Those patients with anti-RNA polymerase I antibodies also have severe disease, including: diffuse skin involvement; frequent tendon and joint changes; and frequent internal organ involvement, including renal crises. The PM-Scl antigen is a complex of 11 to 16 proteins that range from 20 to 110 kilodalton (kd) in molecular weight and whose function is not yet known (39). PM-1 antibodies, first identified in polymyositis patients in 1977 (40), were later demonstrated to contain two or more antibodies. One of these was named PM-Scl because it was frequently found in sera of patients with polymyositis-scleroderma overlap syndrome (41). The antibody was later demonstrated in patients with pure polymyositis / dermatomyositis and in patients with scleroderma without myositis (41, 42).

In a study involving 617 patients, PM-Scl antibodies were found in 24% of myositis-scleroderma overlap patients, 5% of patients with polymyositis/dermatomyositis, and 2% of scleroderma patients (without myositis) (42). The antibody identifies a subset of scleroderma patients with limited cutaneous involvement, who are more likely to have myositis and/or arthritis (39). These patients generally have no serious visceral involvement and show a favorable response to therapy (43, 44).

The Th/To antigen is a complex of 6 proteins associated with 2 RNAs referred to as 7-2 and 8-2 (39). The 7-2 RNA is identical to the component of the mitochondrial RNA-processing enzyme known as Rnase MRP (45). The 8-2 RNA is identical to the RNA component of Rnase P, a processing enzyme for all precursor transfer RNA transcripts (46). The antibody is specific for scleroderma or for scleroderma-related disorders such as Raynaud's phenomenon (47). Approximately 2–4% of scleroderma patients are positive for this antibody, and these patients have limited skin involvement (47, 48).

Fcγ Receptor Autoantibodies

It has recently been shown that autoantibodies against the Fcγ receptor are present in the serum of patients with systemic lupus erythematosus, Sjögren's syndrome and scleroderma (49). Fcγ receptors are members of the immunoglobulin supergene family and are present in a variety of cells, including macrophages, natural killer cells, monocytes, neutrophils, platelets and B-lymphocytes. The Fcγ receptor is specific for immunoglobulin G (IgG) and plays an important role in removing immune complexes from the circulation. Furthermore, when Fcγ receptors bind to the ligands, they stimulate cells to release various cytokines (interleukin [IL]-2, IgG, TNF, etc.) and a variety of prostaglandins. In a recent study, it was shown that 66% of patients with systemic scleroderma and 32% with localized scleroderma have circulating antibodies against the Fcγ receptor (50). Autoantibodies against the Fcγ receptor were found in association with Scl-70 or anticentromere autoantibodies. However, the presence of Fcγ receptor autoantibodies did not correlate with duration of disease, clinical picture or other laboratory data. Furthermore, these autoantibodies are not markers for scleroderma. Yet, they may play a role in its pathogenesis by causing the release of cytokines that may contribute to vascular changes and fibrosis.

Cellular Immunity

The role of cellular immunity in the pathophysiology of scleroderma has received considerable attention over the past decade. Several factors suggest that cellular immunity is operative; these include the presence of mononuclear cell infiltrates, altered function of T-helper cells and monocytes, reduced natural killer (NK) cell activity, release of various cytokines, and the presence of autoantigens against various components of the connective tissue (51).

Adhesion molecules play a crucial role in the regulation of the inflammatory reaction.

These molecules, located on endothelial cells, lymphocytes and fibroblasts, mediate cell-cell and cell-matrix interactions (Fig. 2). Recruitment of activated lymphocytes into the tissues affected by scleroderma may be explained, in part, by aberrant expression of these molecules.

Expression of Adhesion Molecules

Three major families of adhesion molecules have been defined: the selectins, integrins and members of the immunoglobulin (Ig) superfamily. Each family demonstrates increased expression in scleroderma, indicating an increase in the activity of the cells bearing those molecules.

Selectins

The initial contact of leukocytes with endothelial cells is mediated primarily by the selectin superfamily of adhesion molecules. Rapid expression of E-selectin and P-selectin occurs after initial stimulation of endothelial cells by a leukocyte (Fig. 2). Endothelial cells in the skin and minor salivary glands of patients with scleroderma show an increased expression of E-selectin. The intensity of the mononuclear cell infiltrate in the skin of patients with scleroderma correlates with endothelial cell expression of this adhesion molecule (52). Sera from patients with scleroderma show an increase in soluble E-selectin and P-selectin (53).

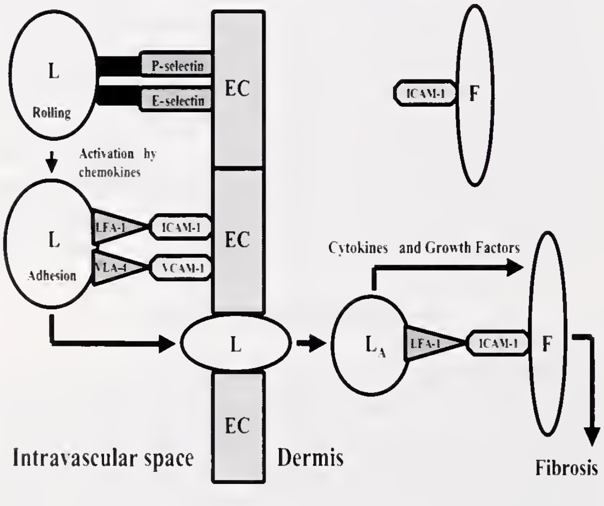

Fig. 2. Role of adhesion molecules in the regulation of the inflammatory reaction in scleroderma. These molecules, located on endothelial cells, leukocytes and fibroblasts, mediate cell-cell and cell-matrix interactions. Abbreviations: L = leukocyte, EC = endothelial cell, L_A = activated leukocyte, F = fibroblast, LFA-1 = leukocyte function associated antigen-1, VLA-4 = very late antigen-4, ICAM-1 = intracellular adhesion molecule-1, and VCAM-1 = vascular cell adhesion molecule-1.

Integrins

Integrins are a family of heterodimeric transmembrane glycoprotein molecules that are assembled from one α and one β subunit. The ligand that binds to a specific integrin receptor is determined by the precise combination of α and β subunits. Integrins serve as a means of communication between extracellular matrix molecules such as collagen, laminin, fibronectin, thrombospondin and vitronectin, through the cell membrane to the intracellular compartment. They also bind receptors of the Ig gene superfamily.

Expression of integrins is increased on endothelial cells, mononuclear infiltrating cells, fibroblasts and dendritic cells in scleroderma skin (52). Endothelial cells have increased expression of β1 integrins, very-late antigen (VLA)-2 and VLA–4 in acute and chronic scleroderma. A moderate number of mononuclear cells in chronic scleroderma and nearly all inflammatory cells in the acute phase of scleroderma express leukocyte function associated antigen (LFA)-1α and/or LFA-1β, members of the β2 integrin family. In contrast, these same integrins are expressed on scattered mononuclear cells in healthy skin. β1 integrin expression, particularly those with the α3 epitope, is increased in dermal fibroblasts and dendritic cells of macrophage origin.

Immunoglobulin Gene Superfamily

Increased expression of integrin receptors on endothelial cells and immunoglobulin (Ig) adhesion molecules on T cells plays a substantial role in the recruitment of T cells to peripheral tissues. Intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are members of the Ig gene superfamily. These molecules play a significant role in the interactions between lymphocytes and endothelial cells or fibroblasts (Fig. 2). While ICAM-1 is located on the cell surface of both endothelial cells and fibroblasts, VCAM-1 is located only on endothelial cells.

Firm adhesion of activated lymphocytes to endothelial cells occurs by interactions between integrin and Ig adhesion molecules. LFA-1 and VLA-4, integrin receptors on lymphocytes, bind to ICAM-1 and VCAM-1, respectively, on endothelial cells. The infiltrating T cells contact and activate fibroblasts by interactions between LFA-1 (located on the activated T-cell) and ICAM-1 (located on the fibroblast).

In acute and chronic scleroderma, the expression of ICAM-1 is increased on both endothelial cells and fibroblasts (52, 54, 55). The increased expression of LFA-1 and ICAM-1 offers one explanation for the increased infiltration of mononuclear cells in biopsies of scleroderma skin (52) and for the increased binding of T-cells to scleroderma fibroblasts relative to control fibroblasts (56). The other major molecule in this family of adhesion molecules, VCAM-1, also shows increased expression on endothelial cells in the skin of patients with scleroderma (57).

Cytokines

It has been hypothesized that, following the activation of lymphocytes and monocytes by an unknown antigen, multiple cytokines are released. These lymphokines and monokines, released into tissues and in the circulation, may damage endothelial cells and modulate behavior of fibroblasts as it relates to proliferation, chemotaxis, migration and synthesis of extracellular matrix elements (Table 2). This leads to massive deposition of newly synthesized connective tissue, fibrosis and concomitant organ insufficiency.

Several cytokines are increased in scleroderma serums, including IL-1, IL-2, IL-4, IL-6, and IL-8. In addition, IL-4, IL-6 and IL-8 have been demonstrated in scleroderma skin. Also, a variety of growth factors were noted in scleroderma skin, including transforming growth factor-β (TGF-β), platelet derived growth factor (PDGF), connective tissue growth factor (CTGF), basic fibroblast growth factor (bFGF) and endothelin-1 (ET-1). It should be noted that although many of the cytokines and growth factors act to promote fibrosis, the effect of others is to hinder it. For example, interferon (IFN)-γ is a potent suppressor of collagen synthesis (Table 2). Finally, the effects of some cytokines are mixed. TNF stimulates the proliferation of fibroblasts. Moreover, it increases endothelial cell expression of adhesion molecules (E-selectin, ICAM-1, VCAM-1) and release of endothelin-1. On the other hand, it decreases fibroblast production of types I and III collagen while promoting collagenase gene induction.

TGF-β

Many studies have focused on the role of TGF-β in the pathogenesis of scleroderma. TGF-β is a growth factor that has pleiomorphic cellular actions, typified by its actions on fibroblasts and endothelial cells. *In vitro*, TGF-β stimulates the synthesis of extracellular matrix (ECM) components, including collagen types I and III, glycosaminoglycans and fibronectin (58–60). It further promotes fibrosis by augmenting the synthesis of inhibitors of matrix metalloproteinases (TIMPs), which inhibit collagenase activity (61). These inhibitors, particularly TIMP-1, are also elevated in the sera of patients with scleroderma (62).

TGF-β may also regulate collagen production indirectly, by its effect on other cytokines and growth factors. For example, PDGF is another growth factor that stimulates fibroblast proliferation and increases collagen synthesis. TGF-β produces upregulation of PDGFα receptors and mRNA upon continual stimulation of scleroderma fibroblasts (63). TGF-β also induces endothelial cell production of endothelin-1, a potent vasoconstrictor that also stimulates production of collagen by fibroblasts.

TABLE 2

Cytokines and Growth Factors Involved in the Regulation of the Biological Behavior of Fibroblasts (39)

Biological Effect	Cytokine / Growth Factor
1. Increased collagen synthesis	TGF-β; PDGF; IL-1; IL-4; IL-6;
2. Decreased collagen synthesis	IFN-β; IFN-γ, TNF-α and β
3. Fibroblast proliferation	IFN-γ and β; TGF-β; PDGF; TNF; IL-1; IL-4;
4. Chemoattraction	TGF-β; IL-4; TNF; PDGF; IFN-γ
5. Glycosaminoglycan synthesis	IL-1; TGF-β; TNF
6. Fibronectin synthesis	TGF-β; IL-4
7. Endothelial cell injury	TNF (α, β); IFN-γ; NK cell; IL-2; granzyme A
8. Reduction of collagenase synthesis	TGF-β
9. Collagenase gene induction	TNF-α

IL = interleukin
TGF = transforming growth factor
PDGF = platelet derived growth factor
TNF = tumor necrosis factor
IFN = interferon
NK = natural killer

However, other effects are less clear in the literature. Some *in vivo* studies have shown fibrotic skin to be lacking TGF-β expression (64), while others have reported an increase (65). There is conflicting data as to whether skin fibroblasts and platelets from patients with scleroderma produce increased amounts of TGF-β (66, 67). Other studies implicate endothelial cells as the source of TGF-β synthesis (68). Despite these inconsistencies in the literature, TGF-β remains a model candidate as a mediator of fibrosis in scleroderma.

Chemokines

Chemotactic cytokines, secreted primarily by leukocytes and related by a conserved four-cysteine motif, regulate the recruitment of specific leukocytes to inflammatory regions. Recent studies have elaborated abnormalities of several chemokines in patients with scleroderma. Serum levels and spontaneous production levels of monocyte chemotactic protein-1 (MCP-1, an attractant for monocytes) and macrophage inflammatory protein-1α and β (MIP-1 α and β, attractants for monocytes and type-1 T helper cells) are elevated in scleroderma patients (69). Elevated serum levels of MCP-1 and MIP-1α correlate with the presence of pulmonary fibrosis (69).

MCP-1 shows greater expression in the epidermis, inflammatory mononuclear cells and endothelial cells of the sclerotic skin from patients with scleroderma compared to those with normal skin (69). Abnormal recruitment of macrophages and the consequent release of cytokines/growth factors by these cells is one possible mechanism by which MCP-1 may contribute to fibrosis of the skin. It is noteworthy that TGF-β is also secreted from macrophages (70). Upregulation of this growth factor has been proposed as the indirect method by which MCP-1 stimulates collagen synthesis by fibroblasts (71).

Cellular Cytotoxicity

Studies investigating cellular cytotoxicity in scleroderma are relatively few in number. Cytolytic CD8$^+$ T cells may contribute to endothelial cell injury in scleroderma by releasing granzyme A. Levels of this serine protease have been found to be elevated in the sera of patients with scleroderma (72).

Pathogenesis of Scleroderma — Current Concepts

A recent study investigated the theory that fetal antimaternal graft versus host reactions may be involved in the pathogenesis of scleroderma in some women (73). The study demonstrated Y-chromosome sequences in DNA from peripheral-blood cells in 32 of 69 women with systemic sclerosis (46%), as compared with 1 of 25 normal women (4%). Moreover, skin biopsy specimens from 19 women with scleroderma demonstrated Y-chromosome sequences in 11 specimens. The authors postulated that scleroderma is initiated in some women by fetal cells that cross the placenta during pregnancy. A subsequent environmental exposure (viral or chemical) then activates these cells, which launch the series of events that results in scleroderma. Although the theory implicating cellular microchimerism is attractive, the study offered no data to explain the occurrence of scleroderma in men, or in women who have never had children.

Conclusions

Research continues to contribute to our understanding of the immunopathogenesis of scleroderma. Inevitably, additional adhesion molecules, cytokines, growth factors, and chemokines will be identified. Some of these may play more substantial roles than those presently being investigated. Further elucidation of the events that precipitate the initial activation of the immune system in this disease will be crucial for both basic research and clinical practice.

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Skin Cancer:

A Review and Atlas for the Medical Provider

Ron M. Shelton, M.D.

Abstract

Skin cancer is increasing in prevalence and is the most common form of cancer in young individuals. Descriptions of the clinical presentations of the most common skin cancers were derived from the author's clinical experience and a review of the literature. Photographs depicting the typical appearance of these lesions were collected, to facilitate recognition. Unique clinical characteristics of skin malignancy are described in the text and illustrated with photographs of the most typical presentation(s) of each of the common skin cancers. Early recognition leads to cure in most cases.

Key Words: Skin cancer, basal cell carcinoma, squamous cell carcinoma, actinic keratosis, melanoma, 5-fluorouracil, Mohs', micrographic surgery, curettage, electrodesiccation, Hutchinson sign, cryotherapy.

The prevalence of skin cancer in the United States is increasing at an alarming rate. Since 1974, about 1.2 million cases of nonmelanoma skin cancer (1) and more than 27,000 cases of melanoma (2) have been diagnosed each year. More recently, this latter figure has been shown to be an underestimate. An American Academy of Dermatology survey suggested that a more probable number of cases of melanoma might be close to 80,000 per year (3). Although some of this increase may be due to earlier detection or previous underreporting of melanoma cases, it is unlikely to be due to changes in diagnostic criteria by pathologists and probably represents a real increase in melanoma cases (4). The 1.2 million prevalence figure for non-melanoma skin cancer approximates the frequency of all other cancers combined. By the year 2001, the lifetime risk of an individual for developing malignant melanoma will be 1:75 (3).

The greatest cause of this increase hinges on the positive social attitude toward sun exposure during the last half century. This is a more important factor than any decrease in the ozone layer (5). Fair-skinned individuals with red or blond hair and blue eyes, and with Irish, Scottish, English or Welsh background are particularly susceptible. Rarely, inherited syndromes, such as xeroderma pigmentosum, epidermodysplasia verruciformis, familial atypical mole syndrome and Gorlin-Goltz (basal cell nevus) syndrome and others, predispose individuals to skin cancer, but sun exposure remains a significant co-factor.

The great majority of skin cancers could be prevented if better sun protection techniques were used.

Basal Cell Carcinoma

Basal cell carcinoma (BCC), the most prevalent type of skin cancer, develops *de novo* without a precursor clinical stage. Eighty percent of these skin cancers occur on the head and neck, and the prevalence is roughly equal in men and woman. Twenty percent of individuals having a BCC are less than 50 years of age. A Caucasian person has a 33% lifetime risk of acquiring a BCC. Basal cell carcinoma is extremely uncommon in darker skinned individuals but does occur occasionally. An African study found a race-specific mean annual incidence rate per million population of 58.5 in Caucasians and 0.065 in native Africans (6).

Basal cell carcinoma rarely metastasizes (approximately 1:100,000). The few that do are those that have recurred repeatedly following treatment or those that have been present for several decades. Fatalities are very rare and usually occur at an average age of 85, with refusal of treatment as the cause in 40% these cases (7).

Clinical Characteristics of BCC

The superficial type of BCC usually occurs on the trunk as an erythematous macule or patch that may be mistaken for eczema. A

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pathognomonic finding is a translucent border, often with telangiectases (Fig. 1). Histologically, one finds nests of basaloid cells lined up at the periphery in a palisading array. Often there is a retraction artifact of the stroma beyond the neoplasm, creating a clear space. Superficial BCCs located on the face may have more of an infiltrative pattern histologically, with strands of neoplasm interspersed in the stroma. They are often larger than is clinically apparent. Nodular BCCs demonstrate translucency and telangiectases, and often have a central indentation (Fig. 2). These neoplasms histologically involve the dermis and can invade more deeply at times. They can become large in size, usually as a result of patient neglect (Fig. 3). Ulceration may be limited, or in some cases more extensive, especially in larger lesions (Fig. 4). It is not uncommon for early lesions to erode and bleed, only to heal sponta-

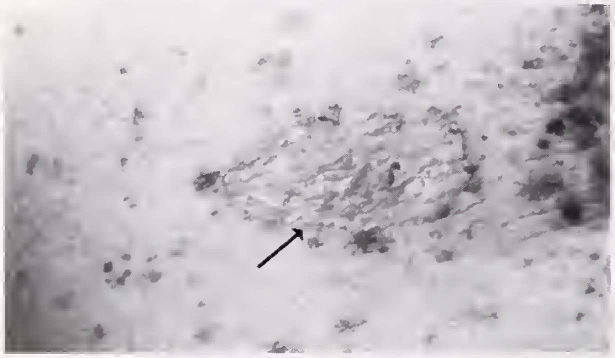

Fig. 1. Superficial basal cell carcinoma on the trunk. Note translucent edge (arrow).

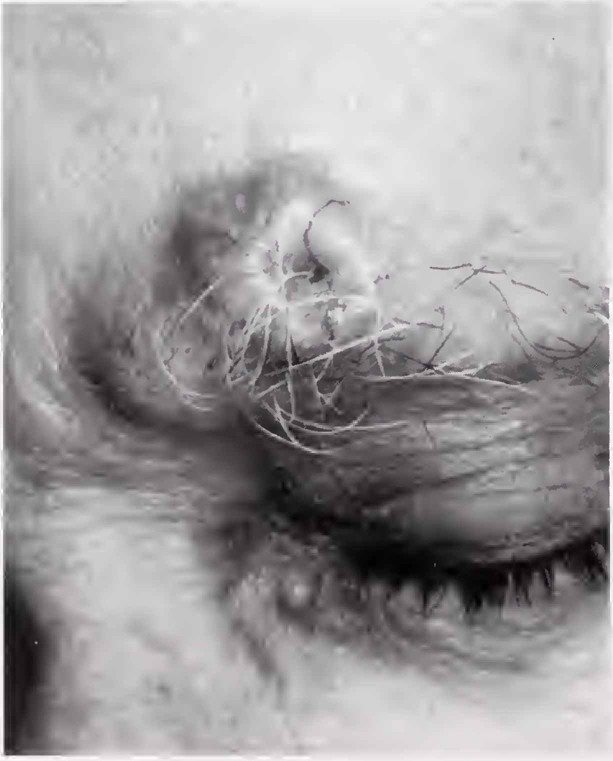

Fig. 2. Nodular basal cell carcinoma of the suprabrow with central indentation and telangiectases within the translucent lesion.

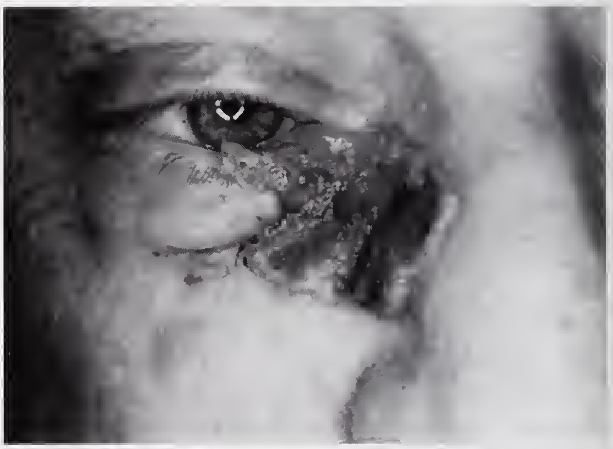

Fig. 3. Neglected exophytic basal cell carcinoma of the medial canthus and palpebral margin.

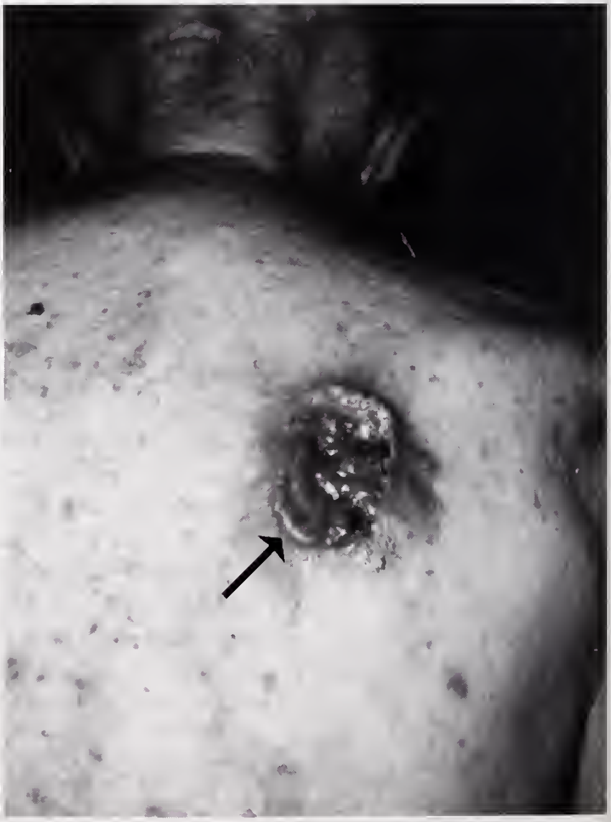

Fig. 4. Large, neglected ulcerated basal cell carcinoma misdiagnosed as squamous cell carcinoma by several physicians who did not note the translucent border (arrow).

neously. This may support the patient's denial and create a longer delay before treatment is sought.

Keratotic BCCs demonstrate milia and have a rougher surface than the typical nodular BCC. BCCs can be pigmented (Fig. 5) and may suggest a diagnosis of malignant melanoma. Such pigmented BCCs occur more commonly in dark-complected Caucasian individuals.

Basal cell carcinoma may display aggressive growth patterns, including infiltrative micronodules with squamous differentiation (metatypical or basosquamous cell carcinomas) and morpheaform (morphemic or sclerosing BCC). Sclerosing BCCs typically grow as one- or two-cell thick strands in a sclerotic stroma and are difficult to detect clinically. Diagnosis is often delayed until a secondary change, such as bleeding, occurs (Fig. 6) many years later. The dermis is invaded for a considerable distance beyond the normal-appearing, overlying epidermis. Surgical defects after complete extirpation of sclerosing BCC are often quite extensive (Fig. 7), but reconstruction can provide a satisfactory result.

Aside from the above histologic patterns, other criteria such as large size, ill-defined border(s), young age of the patient, immunocompromised host, recurrence, locally persistent "H- zone" (ears, eyelids, nose, lips) and scalp lesions, and dysesthesia indicative of perineural or intraneural invasion, may indicate that a BCC will be more aggressive. While less than 2% of BCCs occur in sun-protected areas such as the axilla (Fig. 8) or groin, these lesions often display more aggressive behavior than those in sun-exposed locations.

Although most BCCs are caused by ultraviolet damage, some develop within congenital precursor lesions such as nevus sebaceous of Jadassohn (Fig. 9). This yellowish, shiny plaque occurs on the scalp, head, and/or neck of neonates, or develops within the first few years of life. Because there is about a 3% risk of developing BCC within a nevus sebaceous during the lifetime of the individual, elective prophy-

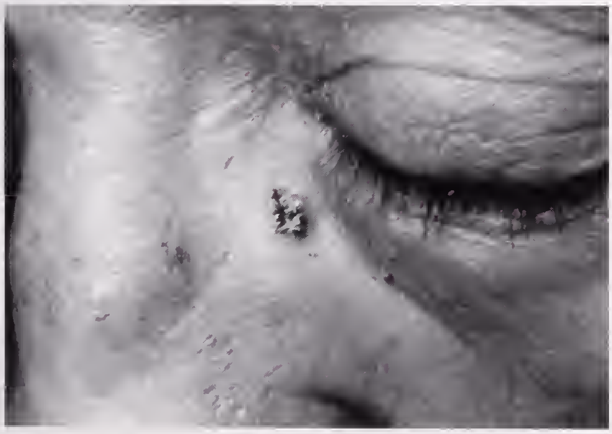

Fig. 5. Pigmented basal cell carcinoma with black coloration and translucent edge.

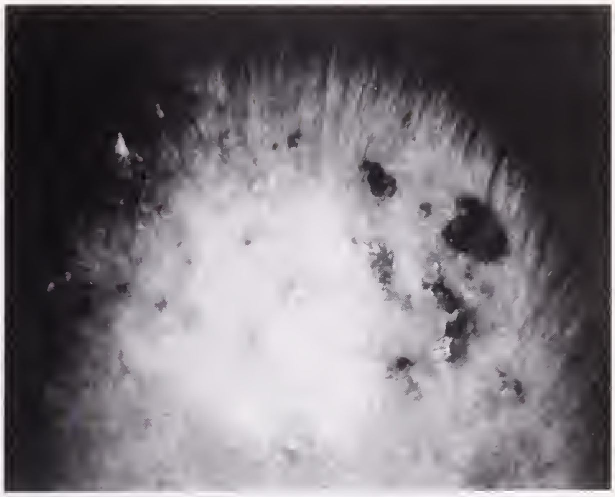

Fig. 6. Large, undetected basal cell carcinoma which involved most of the scalp. It was diagnosed only after the lesion bled. This was found to be a morpheaform basal cell carcinoma.

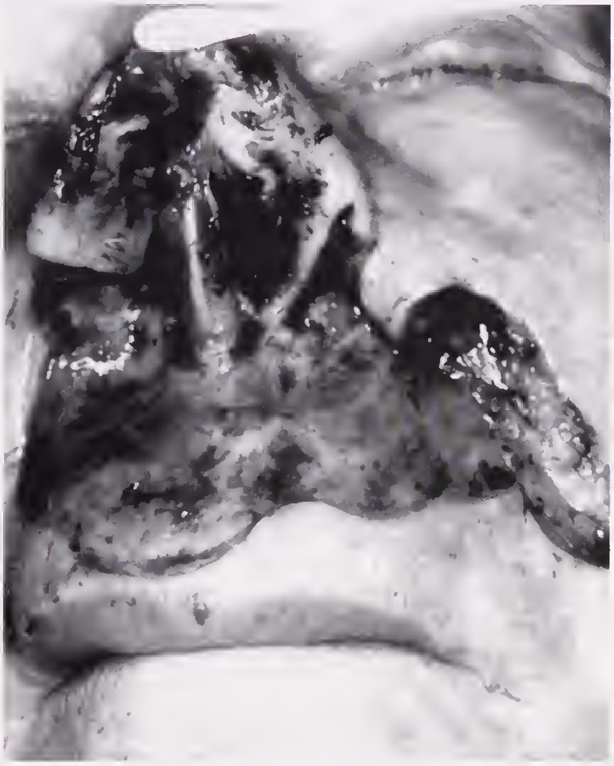

Fig. 7. Recurrent sclerotic basal cell carcinoma of the upper lip — Mohs' micrographic surgical defect.

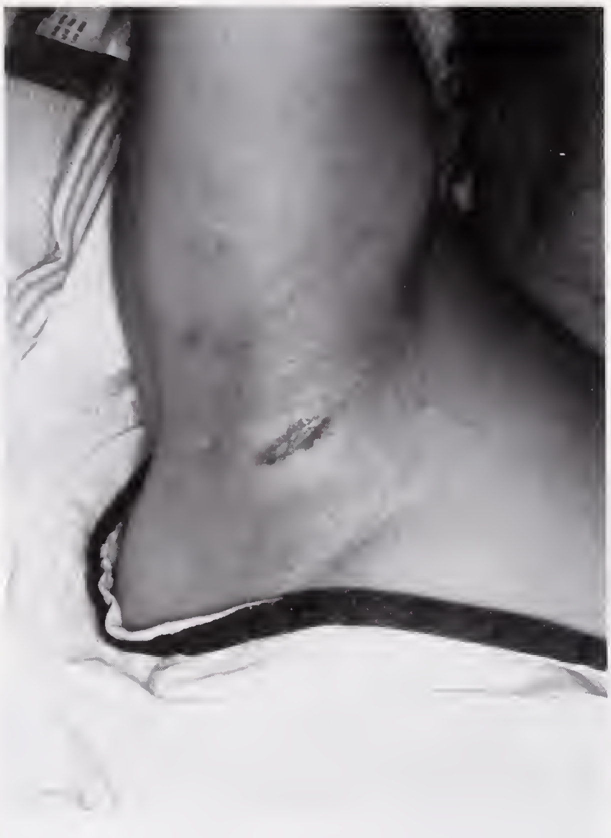

Fig. 8. Axillary basal cell carcinoma.

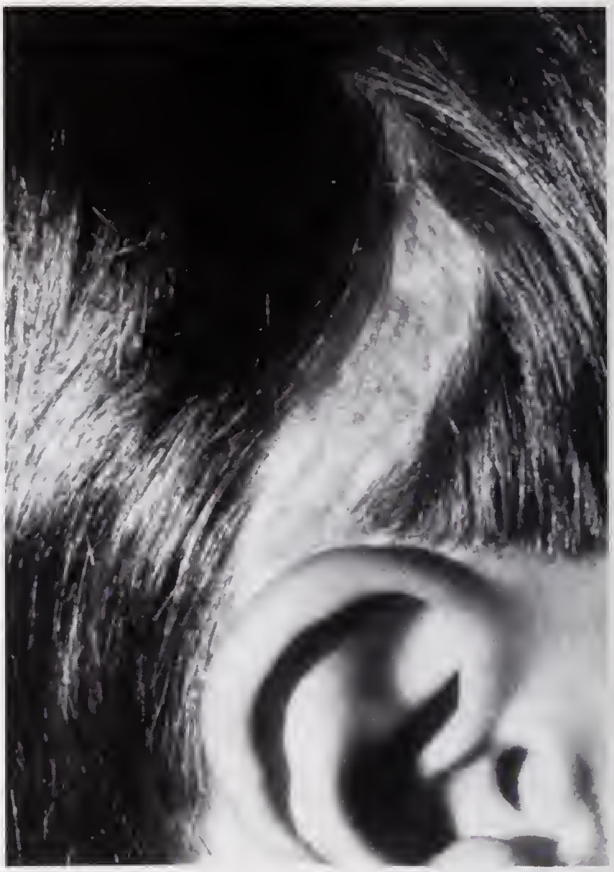

Fig. 9. Nevus sebaceus of Jadassohn in an adolescent.

lactic excision is usually recommended after puberty. Other neoplasms that can develop in a nevus sebaceous include squamous cell carcinoma and syringocystadenoma papilliferum, a sweat gland tumor.

Patients with the autosomal, dominantly inherited basal-cell nevus syndrome (Gorlin-Goltz syndrome) often develop hundreds of BCCs (Fig. 10). Extracutaneous findings include characteristic facies, odontogenic keratocysts, calcification of the falx cerebri, bifid ribs and palmar pits. Basal cell carcinomas in this syndrome usually have their onset in adolescence.

Treatment of BCC

Therapy for BCCs includes curettage and electrodesiccation, liquid nitrogen cryotherapy, excision with standard histopathologic margin analysis, modified frozen analysis, and radiation therapy. Mohs' micrographic excision is reserved for aggressive BCCs in all sites, or smaller lesions in areas where tissue conservation is crucial, such as eyelids, nose, lips, ears, digits and genitalia. Mohs' micrographic surgery is an in-office procedure that provides the highest chance of local cure. Surgical margins are examined by frozen section, and the location of any residual focus of tumor is mapped out. In this way, the entire neoplasm may be removed precisely without removal of excessive, uninvolved surrounding tissue.

Actinic Keratosis

Although not a malignancy per se, an actinic keratosis (AK) is a potential precursor lesion to squamous cell carcinoma (SCC). AKs are the most common lesions found on photodamaged skin. They may resolve spontaneously, especially if sun-screen is used, but 6–10% of patients with AKs may develop an SCC within ten years (8).

Characteristics of AK

AKs appear as small, erythematous, keratotic papules, often more readily detected by palpation than by their visual appearance. Fair-skinned individuals may have hundreds of such lesions. Because progression to SCC can occur in some cases, persistent and enlarging lesions should be treated. The epidermis of an AK demonstrates

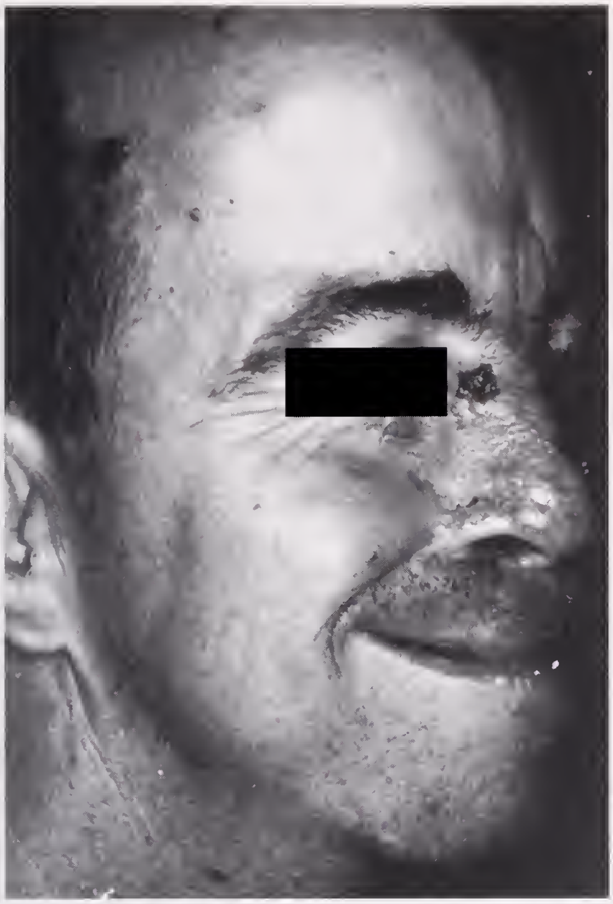

Fig. 10. Basal cell nevus syndrome (Gorlin-Goltz).

partial thickness atypia of keratinocytes, beginning at the basal layer but not reaching the stratum granulosum. There is usually focal parakeratosis (retained nuclei in the stratum corneum).

Treatment of AK

AKs are commonly treated using liquid nitrogen cryotherapy or curettage and electrodesiccation. Topical 5-fluorouracil (5-FU) solution or cream may also be used to chemically remove visible keratoses, as well as those that exist microscopically but are not yet clinically apparent. This is an excellent treatment for patients with myriad lesions for which cryotherapy would be impractical or too painful (Fig. 11). The marked erythema, vesiculation, and crusting, as well as possible discomfort that occurs with topical 5-FU, should be explained to the patient prior to initiating therapy.

Squamous Cell Carcinoma, *In Situ*

Intraepidermal squamous cell carcinoma (Bowen's disease) can be viewed as the next step in the progression of atypia before a lesion develops into a frankly invasive SCC. This lesion sometimes may be located on the sun-exposed areas of the head, neck, trunk, and legs. "Erythroplasia of Queyrat" refers to Bowen's disease occurring on the genitalia. In some instances, periungual Bowen's disease has been demonstrated to harbor human papilloma virus similar to the subtypes that have been implicated as the cause of cervical carcinoma. Bowen's disease on non-sun-exposed areas has been noted to occur with previous arsenical ingestion and may also be associated with internal malignancy (9).

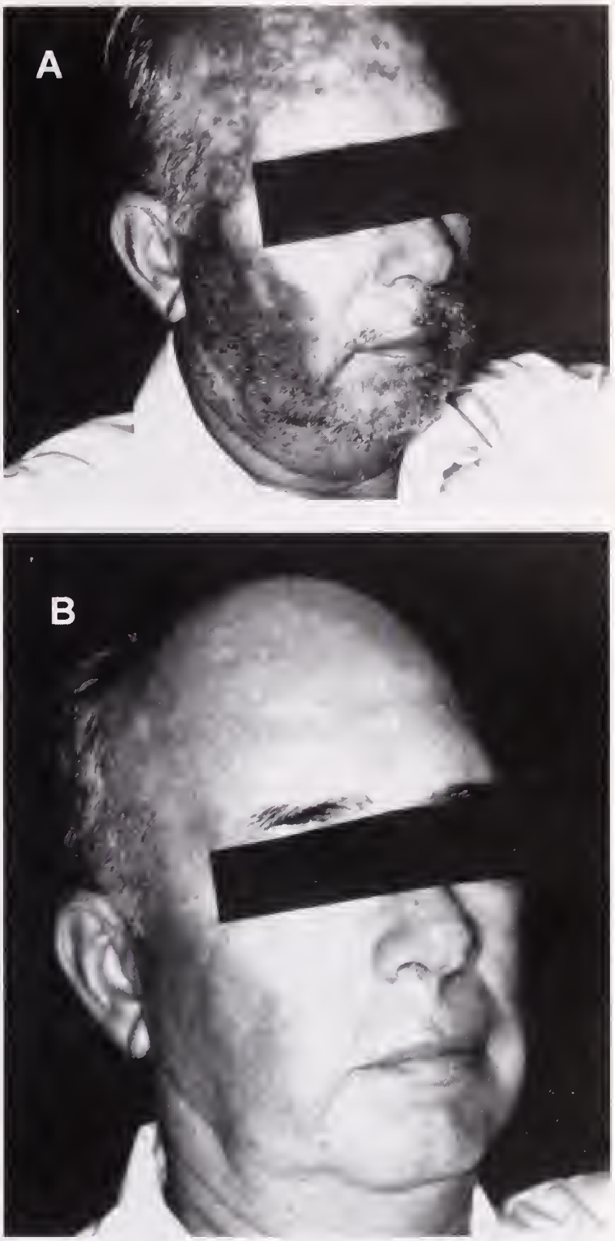

Fig. 11. **A.** Multiple actinic keratoses highlighted by the use of 5-fluorouracil (5-FU) for two weeks. **B.** One month after completion of a four-week course of 5-FU.

Appearance of SCC *In Situ*

SCC *in situ* appears as a velvety, erythematous, slightly keratotic and barely elevated papule or plaque. When located on the glans penis it usually lacks a significant keratotic surface (Fig. 12). The absence of translucency in Bowen's disease is helpful in differentiating it from the superficial type of BCC. Bowen's lesions are usually greater in diameter than AKs and tend to persist for months or years before diagnosis. They are sometimes misdiagnosed as localized eczema. Histologically, there is full thickness atypia, in contrast with AKs. The pathology may extend down into the epithelium of the adnexa.

Treatment of SCC *In Situ* (Bowen's Disease)

Cryotherapy, 5-FU, curettage and electrodesiccation, laser ablation and dermabrasion have been used, but are superficial in their effects and may not remove deeper extensions of disease in the epithelium of the adnexa, e.g., hair follicles. Surgical excision, radiation therapy, and Mohs' micrographic excision are alternatives to the more superficial treatments and are preferable. Mohs' micrographic surgery is especially helpful for tissue conservation when the digits or genitalia are involved.

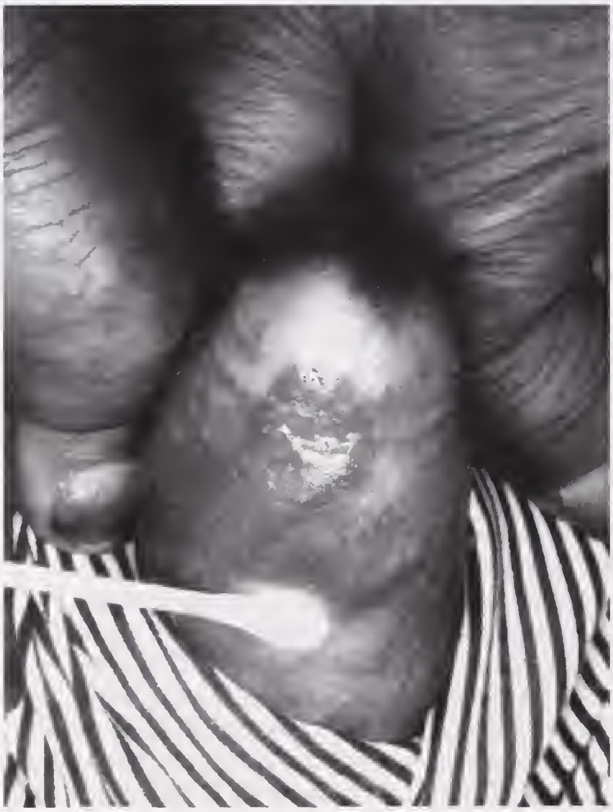

Fig. 12. Squamous cell carcinoma *in situ* of the glans penis does not display as much of the keratotic surface as it does in non-glabrous skin.

Squamous Cell Carcinoma

Approximately 50% of squamous cell carcinomas (SCC) develop on the head and neck. They are much less prevalent than BCC (1:5) and are approximately four times more common in men than in women. Most lesions occur in individuals over 50 years of age. Caucasians may have as much as a 10% lifetime risk of developing SCC. The mortality rate from this type of carcinoma is approximately 1:100,000 (7). Forty-seven percent of these mortalities occur in patients whose SCC arose on the ear. Higher risk of metastasis occurs with lesions located on the scalp and lip regions as well as on the ear.

Characteristics of SCC

SCCs are keratotic papules or nodules (Fig. 13) which may ulcerate. Histologically, these skin cancers demonstrate invasion of atypical keratinocytes into the dermis. Nests of atypical keratinocytes may be well- or poorly-differentiated. Should there be extensive hyperkeratosis, a cutaneous "horn" may develop (Fig. 14).

Treatment of SCC

Once the diagnosis of squamous cell carcinoma is established, it is important to examine the regional lymph nodes to check for possible metastases. The modalities of therapy for SCC are similar to those used in treating BCCs, except that wider margins are generally used. Ablative therapy such as curettage and electro-

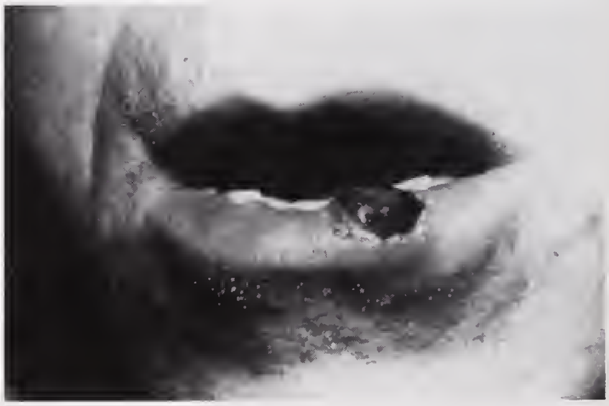

Fig. 13. Squamous cell carcinoma of the lower vermillion lip.

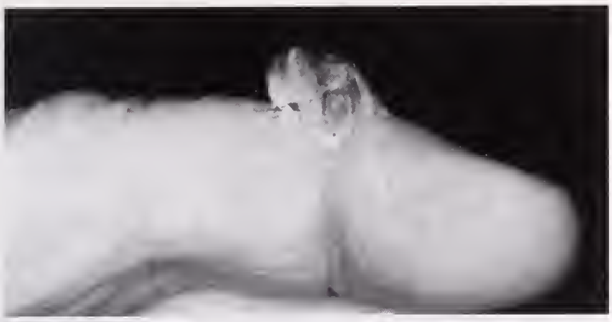

Fig. 14. Cutaneous horn of the digit surprisingly proved to be only a hypertrophic actinic keratosis and not a squamous cell carcinoma.

desiccation or cryosurgery may not eradicate deeper pathology and may increase the risk of persistent disease and eventual metastasis. Should cryotherapy or curettage and electrodesiccation be employed in treating SCCs, follow-up is mandatory. Radiation therapy may be used as a solitary treatment in patients whose medical condition precludes surgery, or if the lesion is inoperable. Aggressive SCCs, especially those with perineural or intraneural invasion, can be treated with postoperative radiation as an adjunctive therapy after Mohs' micrographic surgery.

Melanoma

Malignant melanoma is the most dangerous skin cancer, and if not detected early may metastasize with fatal consequences. Prior to the development of invasive melanoma, a forerunner or *in-situ* phase may occur, in which horizontal extension occurs at or above the dermoepidermal junction. In one form, lentigo maligna, this may manifest as a large tan or brown patch on the face, enlarging very slowly for one or two decades, before being diagnosed. It is not unusual for such lesions to have been biopsied several years previously without revealing definitive pathology (Fig. 15). Lentigo maligna, or Hutchinson's freckle, is a melanoma *in situ* that may become invasive at any time. It often presents a difficult management problem, as surgical treatment may replace a precursor lesion with a disfiguring scar. Moreover, the adjacent facial skin is similarly photodamaged and may harbor atypical hyperplastic melanocytes, which may eventually give rise to new melanoma-*in-situ* lesions. This possibility should not lead the physician to excise too widely to eradicate this field effect, since much of the exposed facial skin may harbor such atypical cells.

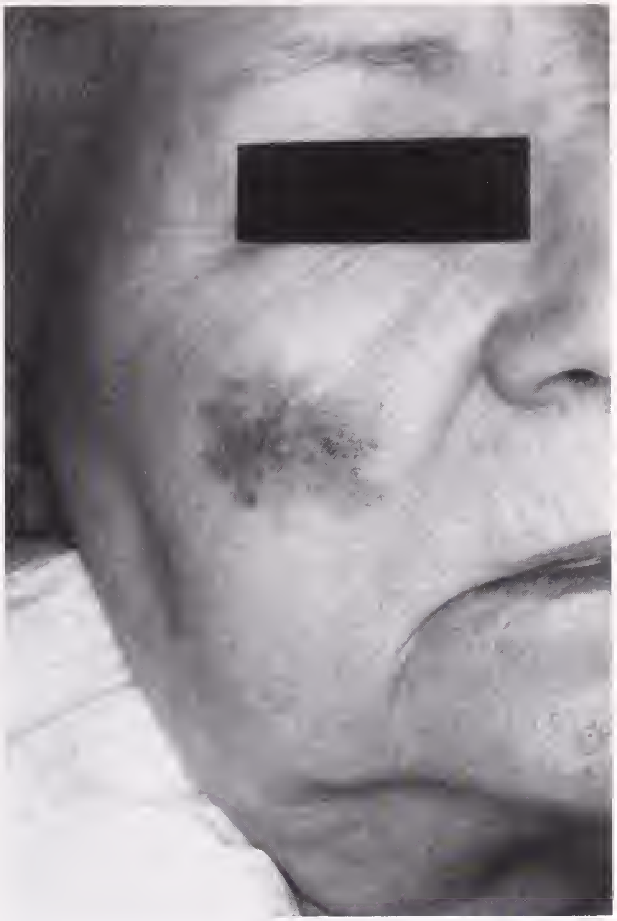

Fig. 15. Melanoma *in situ* of the cheek present for more than ten years. Biopsies on two occasions previously failed to disclose its presence.

Characteristics of Melanoma

Malignant melanoma occurs mostly on the upper trunk, forearms, and legs, usually as an oval or polycyclic, irregularly bordered, variegated and often asymmetric patch (Fig. 16). Approximately 75% of melanomas are superficial. Clinical regression can occur as a result of a localized immunologic reaction. When this occurs, the lesion may develop areas of clearing or whiteness (Fig. 17). Regression is thought by some to indicate a poorer prognosis, but this is controversial.

Lentigo maligna melanoma, representing approximately 5% of melanomas, refers to a Hutchinson's freckle (lentigo maligna) which has developed an invasive component. Fourteen percent of melanomas are of the nodular type. They may develop from the vertical growth phase that occurs after horizontal extension in a preexisting lesion (Fig. 18), or *de novo*. The depth of invasion can be considerable in advanced disease.

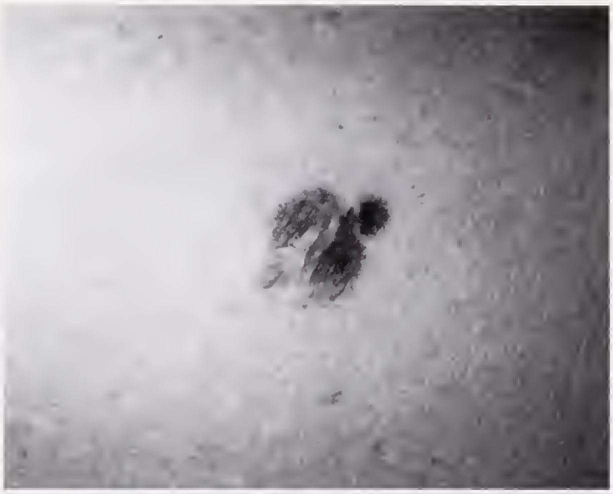

Fig. 16. Asymmetry of a melanoma *in situ.*

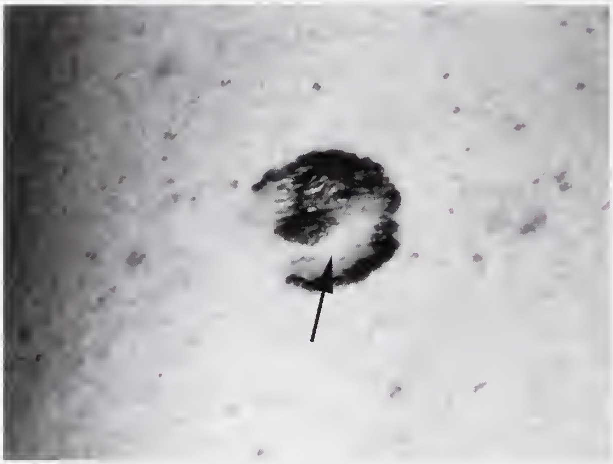

Fig. 17. Regression of a melanoma displaying whitened areas (arrow). (Courtesy of Stuart Salasche, M.D., Tucson, AZ.)

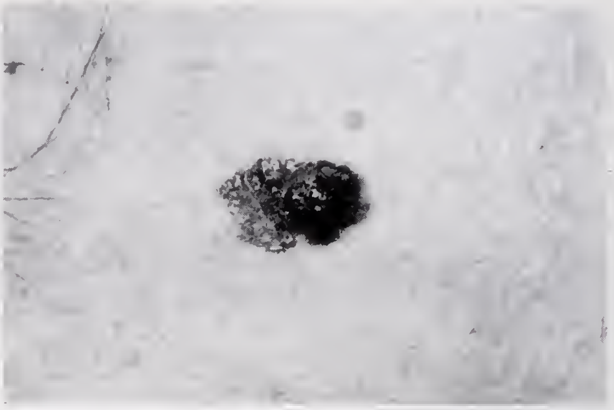

Fig. 18. Nodular melanoma.

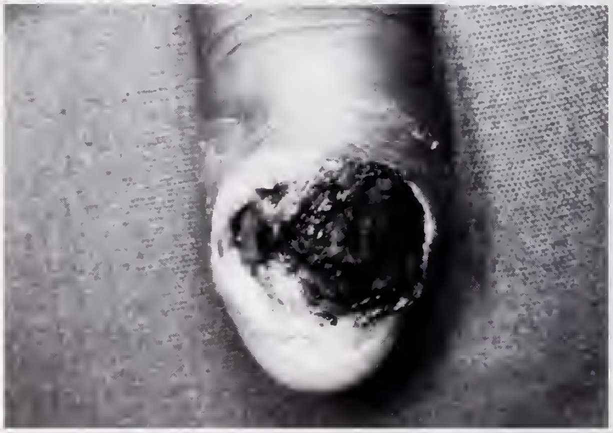

Fig. 19. Subungual melanoma misdiagnosed as osteomyelitis.

Acral-lentiginous melanomas comprise 5% of all melanomas and arise most commonly in patients aged 55–60. Although melanoma is less common in African Americans, 50% of melanomas which do occur in African Americans or Asians are of the acral-lentiginous type. There is usually significant delay in diagnosis, as these lesions are often initially misdiagnosed as subungual fungal disease, eczema, or infection. When they are finally diagnosed correctly, they may have developed nodules and a deeper level of invasion, and have a worse prognosis (Fig. 19). Pigmentation usually seen on the proximal and infrequently seen on the lateral nail fold has been considered by some to be pathognomonic of subungual melanoma, and is often designated "Hutchinson's sign."

Amelanotic melanoma, a rare non-pigmented variant of malignant melanoma, is frequently misdiagnosed as an inflammatory condition such as eczema (Fig. 20), as a benign pyogenic granuloma (Fig. 21), or as actinic keratosis or Bowen's disease. Metastases of malignant melanoma may also be amelanotic. Another rare form of melanoma is the desmoplastic type, an aggressive variant that typically occurs on photodamaged facial skin, especially in women. It has an ill-defined border with gray-stippled dark papules. Histologically, the presence of spindle cells confuses the diagnosis, and special stains are often needed to identify the lesion as a melanoma.

The growth of some melanomas may be hormone-mediated. Normal nevi have been noted to change during pregnancy, and there is some question as to whether there is an increased risk of metastasis of primary melanoma in a pregnant woman. If a suspicious lesion is noted on examination of a pregnant patient (Fig. 22), the physician should not hesitate to

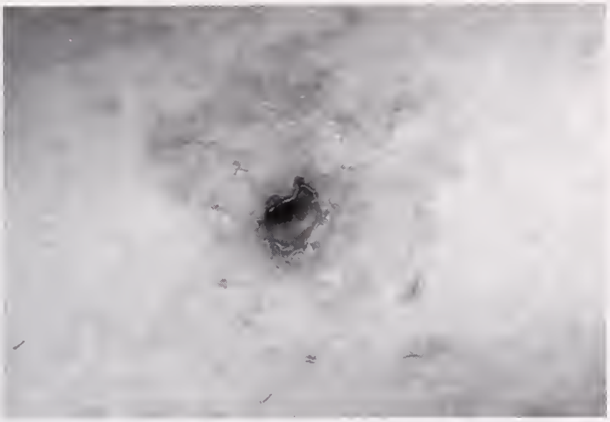

Fig. 20. Amelanotic melanoma misdiagnosed as eczema.

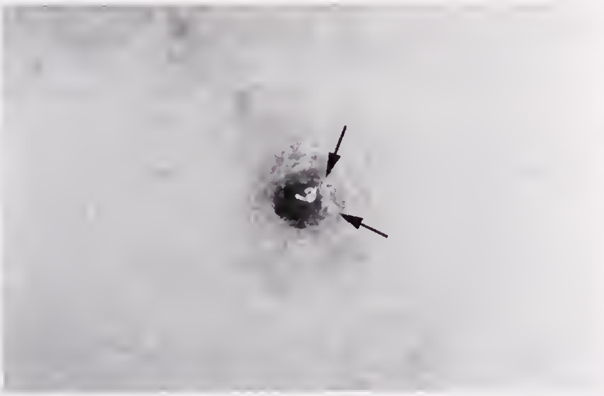

Fig. 21. Amelanotic melanoma appearing as a pyogenic granuloma, displaying a glistening capsule and a peripheral collarette (arrows).

remove it and should then consult with the patient's obstetrician.

Another difficult problem faced by dermatologists is the management of giant congenital nevi. Patients with giant, congenital, hairy "bathing trunk" nevi have a greater chance of developing malignant melanoma within such a lesion than do those with normal, acquired nevi. Local recurrences of giant congenital nevi have been observed even after extensive, multiple-stage excisions, since melanocytes may extend deeply, even into the underlying muscle. Superficial treatment with dermabrasion and laser ablation is not appropriate, since it will not remove pathology that extends deeply around the appendages and into the reticular dermis. Small congenital nevi usually do not pose a significantly greater risk of developing into melanoma (Fig. 23), and determining the necessity for excision should be based on the circumstances of the individual case.

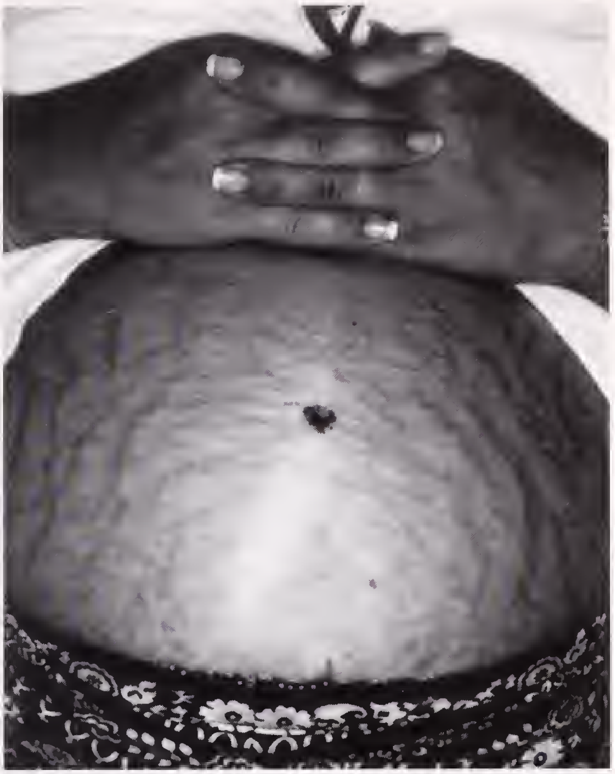

Fig. 22. Melanoma *in situ* which developed in a pregnant patient.

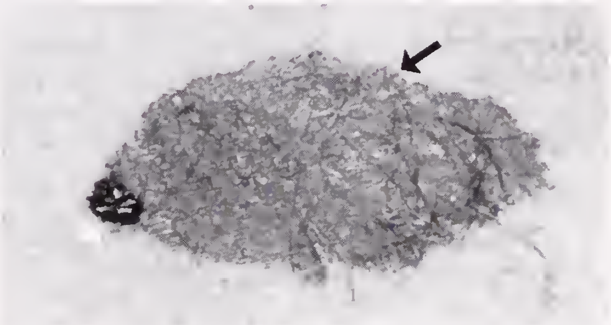

Fig. 23. Melanoma, 1.0 mm (white arrow) deep, arising within a congenital nevus (black arrow).

Treatment of Melanoma

The treatment of choice for malignant melanoma is excision, with clear margins that are based on the thickness of the lesion (Breslow depth). The standard of care for excision is a 0.5 cm margin for melanoma *in situ*, 1 cm for lesions less than 1.0 mm in depth and 2–3 cm for deeper lesions (10). Cosmetic considerations may dictate the use of margins less than 0.5 cm for facial *in-situ* melanomas. If histopathologic examination following initial excision reveals inadequate surgical margins, re-excision is performed.

Clark's levels, which grade the depth of a malignant melanoma by the anatomical level of the dermis to which it extends, are not as reliable a prognostic indicator as the Breslow's depth (11). Elective lymph node dissection is not indicated for thin melanomas and is not helpful in thick tumors. It may be useful in providing prognostic information in cases of moderately deep melanoma. Increasing use of the sentinel node biopsy is helpful in minimizing the morbidity associated with extensive lymph node resection. Adjunctive therapy, including hyperthermic limb perfusion, cryotherapy, radiation therapy, chemotherapy, and vaccination therapy, are still being explored.

Conclusion

The easiest way to decrease the risk of skin cancer is to protect the skin from sun exposure. The 20–30 years of lag period that exists between exposure to harmful solar rays and the subsequent development of skin cancer can lull patients into a false sense of security regarding sunbathing. It is imperative that steps be taken to protect the skin at an early age, while ensuring that enough vitamin D is consumed in the diet. Such measures include sun avoidance between the hours of 10 A.M. and 3 P.M., the wearing of protective clothing, and the use of sunscreens that block both UV-A and UV-B solar rays.

Most skin cancer, even melanoma, may be fully curable, provided that the diagnosis is made at an early stage. Everyone should perform self-examinations for suspicious moles and other growths, and a full skin examination should be a part of the general physical examination.

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Necrotizing Fasciitis:

A Plea for Early Diagnosis and Treatment

John D. Cunningham, M.D., Lester Silver, M.D.[1], and Donald Rudikoff, M.D.[2]

Abstract

Introduction: Necrotizing fasciitis is an uncommon infectious entity that poses difficult diagnostic and therapeutic management decisions.

Purpose: This paper addresses the presentation, evaluation and management of the patient with a necrotizing soft tissue infection.

Case Report: A 54-year-old man presented to his physician with pain and swelling of the left anterior chest wall following a presumed insect bite several days prior. He was treated with oral antibiotics but returned to the office three days later with increased swelling, pain, and erythema in the axilla. Necrotizing fasciitis was diagnosed. He was hospitalized and taken to the operating room for debridement of the chest wall. Extensive necrosis of the skin, subcutaneous tissue and muscle was encountered. Muscle debridement extended from the pectoralis major and both obliques anteriorly to the latissimus dorsi and para-spinalis muscles posteriorly. Multiple operative debridements were performed over several days. The patient developed septic shock requiring blood pressure support, and multiple organ system failure requiring hemodialysis, prolonged ventilatory support and eventual tracheostomy. Split-thickness skin grafts were placed during the third operative debridement and concluded on the 15th day of hospitalization. The patient eventually recovered and on the 53rd hospital day was transferred to the rehabilitation service, where he spent the next four weeks recovering movement in the left arm.

Conclusion: Necrotizing fasciitis is an infectious entity that requires rapid diagnosis, surgical debridement, and tissue coverage if the patient is to survive.

Key Words: Necrotizing fasciitis, soft tissue infection, myonecrosis, surgical debridement.

Introduction

Necrotizing fasciitis is an uncommon, critically serious infection of the subcutaneous tissue and fascia with relative sparing of the skin and muscle, both of which may be infected secondarily. Necrotizing soft tissue infections (NSTIs) are characterized by subepithelial invasion of the soft tissue by microorganisms, resulting in tissue edema, vascular thrombosis, and lymphocytic infiltration. Muscle necrosis may result from untreated infection. The diagnosis is often missed initially because of the paucity of clinical signs and symptoms or the clinician's lack of familiarity with the condition. Once the diagnosis is suspected, the patient needs to be adequately stabilized and then taken to the operating room for surgical exploration and debridement. Negative outcomes result from delay in diagnosis, inadequate surgical debridement, and complications of sepsis (1–6). The in-hospital mortality rate ranges from 6–33% (1–7); for those patients who do survive, significant disfigurement, disability and long-term rehabilitation are the rule.

Case Report

A 54-year-old, left-handed man developed pain in the left chest wall and shoulder a few days after working in the crawl space of his house. An area of redness, pain, and tenderness on the left chest and axilla was diagnosed as cellulitis due to an insect bite. The patient was started on oral azithromycin and non-steroidal, anti-inflammatory analgesics. He returned three days later and was referred for dermatological consultation where a diagnosis of necrotizing fasciitis was made. The man was agitated, demanding analgesics for severe pain in the left chest that radiated to the back. He momentarily lost consciousness in the dermatologist's office and was rushed to the emergency room.

His past medical history was significant for mild hypertension and an episode of perineal cellulitis two years previously. There was no previous history of diabetes mellitus, corticosteroid use, intravenous drug abuse, alcoholism, or peripheral vascular disease. He was allergic to penicillin.

Physical examination in the emergency room revealed a temperature of 36.5°C, pulse 90, respiratory rate 18, and blood pressure 80/55 mm Hg. The patient was awake but lethargic and there was generalized skin mottling over the entire body. An area of reddish-purple discoloration

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extended over the left axilla to the back and flank (Figs. 1, 2). This area was edematous, boggy and tender to palpation. The remainder of the examination was unremarkable.

Laboratory values on admission were significant for a white blood cell count of 7,600 with 69% band cells, BUN of 32 mg/dL, creatinine of 3.0 mg/dL, and blood sugar of 240 mg/dL. An intravenous catheter was placed in the groin and treatment with vancomycin, aztreonam, and metronidazole was started. After adequate fluid resuscitation, the patient was taken to the operating room for operative debridement by a team of general and plastic surgeons.

In the operating room, he was intubated and positioned in the left lateral decubitus position. An incision was initiated in the left axilla, extended caudad to include the left chest wall down to the groin, and extended posteriorly to the midline of the back. The skin, subcutaneous tissue and muscle were all necrotic and the perforating vessels were thrombosed. The latissimus dorsi, and parts of the serratus, pectoralis major, external oblique and internal oblique were all resected (Figs. 3, 4). The wounds were packed with Betadine-soaked gauze and the patient was

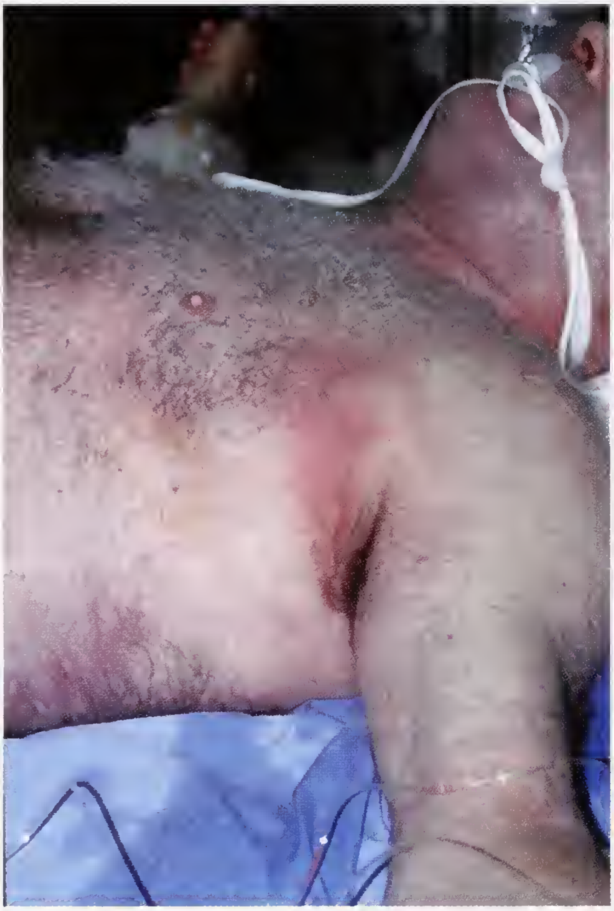

Fig. 1. The patient is supine on the operating room table, intubated, with the left chest exposed showing the area of red-to-purple discoloration in the left axilla.

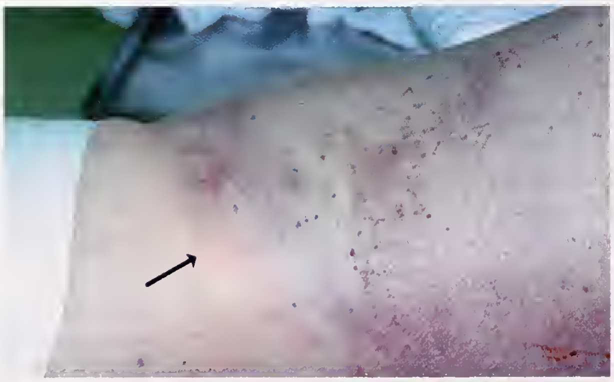

Fig. 2. The patient has been placed in the right lateral decubitus position. Extensive cyanosis is noted on the lower back with an advancing erythematous margin (arrow).

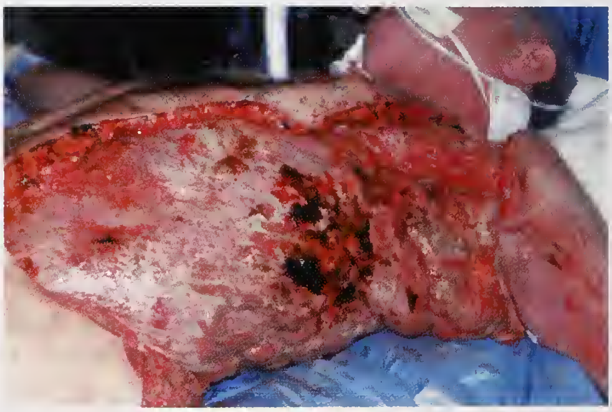

Fig. 3. The patient after complete surgical debridement, with extension of the resection from the left shoulder down, including some of the pectoralis, down to the iliac crest and extending to the midline anteriorly over the abdominal cavity.

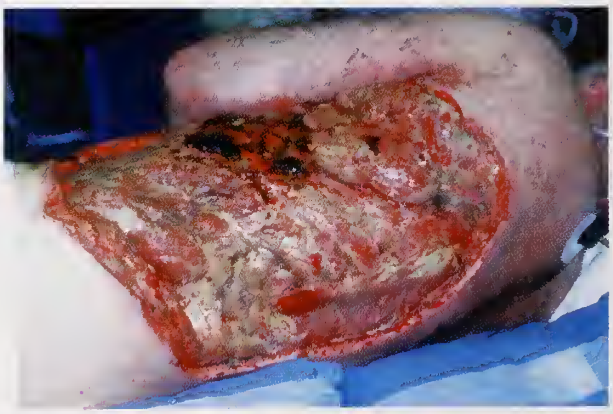

Fig. 4. The patient in the right lateral decubitus position, showing the extensive debridement from the left axilla to the iliac crest.

taken to the surgical intensive care unit. Gram stain from the first operation revealed Gram-positive cocci in clusters, and cultures grew group A beta-hemolytic streptococcus. His condition worsened that night and he was started on intravenous norepinephrine (Levophed®) to maintain a mean blood pressure of 60 – 70 mm Hg. He underwent further debridement on the 2nd and 3rd hospital days; no further infection was noted. On the third day, the wounds were covered in part by split-thickness skin grafts. The patient required three more operative treatments to cover all of the wounds with split-thickness skin grafts. The estimated body surface area that had been debrided and grafted was 18%. Pathological examination showed necrotic skin, adipose tissue and muscle with numerous bacteria.

The patient's overall condition during this time remained critical. Blood pressure support with intravenous norepinephrine (Levophed®) was required for the first nine days in the intensive care unit (ICU). He also received five units of packed red blood cells and six units of fresh frozen plasma. Although urine output was present, his creatinine clearance was low, thereby requiring the use of continuous veno-venous hemo-filtration (CVVH) to remove excess fluid. On the eighth hospital day, when the creatinine clearance improved, CVVH was discontinued. The patient began to show signs of improvement, with resolution of his multi-system organ failure. He remained sedated and intubated for daily bedside dressing changes. Total parenteral nutrition (TPN) was started on the fourth day since attempts at enteral nutrition failed as a result of a paralytic ileus. Enteral nutrition was successfully instituted a few days later and TPN was discontinued. The patient underwent tracheostomy on the 21st hospital day. His course was complicated by an episode of sinus arrest that required a temporary trans-venous pacemaker, and also by Gram-negative line sepsis. After four weeks in the ICU, he was transferred to the surgical floor for an additional two weeks. He then spent another four weeks on the rehabilitation service, improving function in his left hand, arm and shoulder (Fig. 5).

Discussion

NSTIs have been described in the literature for centuries under a variety of names, including malignant ulcer, putrid ulcer, phagedena, Fournier's gangrene and hospital gangrene. A number of retrospective reviews have attempted to distinguish different necrotizing soft tissue infections based on anatomic location, bacterial flora, presence or absence of crepitance, and clinical progression (8). All of these classification schemes serve little purpose, since the initial treatment and management of all NSTIs are the same. Therefore, these sub-categories of NSTIs are important only from an academic point of view and one should maintain a broad therapeutic approach when dealing with any of these infections.

Epidemiology and Pre-existing Conditions

NSTI can occur at any age, including infancy (9). In selected larger series, the youngest person afflicted was 9 years old and the oldest 90, while the mean age varied from 32 years to 57 (1 – 7). The ratio of men to women is 1.4:1 but the reason for this difference is not explained (1 – 7). The majority of patients who develop NSTI have pre-existing conditions that render them susceptible to infection. These conditions may adversely affect their prognosis (1 – 7). The common denominator appears to be an immunosuppressive effect resulting from advanced age, diabetes mellitus, acute or chronic renal failure, local defects such as peripheral vascular disease or lymphedema that predispose to local cellulitis. A list of conditions which have been associated with NSTI is shown in

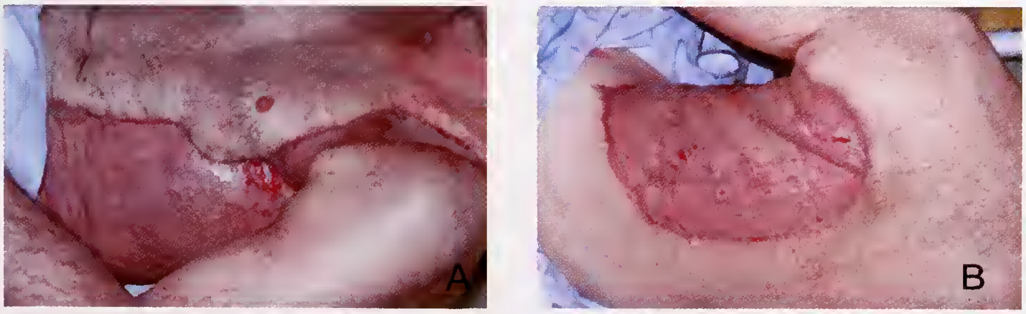

Fig. 5. Anterior (A) and posterior (B) views of the split-thickness skin graft.

Table 1 (1–7). Significant differences in the cause of NSTI exist from study to study and most likely reflect the distinct patient populations seen at each institution. Many patients have more than one pre-existing factor and the number of different factors may be related to outcome (4).

A number of other causes of NSTI have been implicated, as shown in Table 2 in some series (1–7). The etiologies most frequently implicated are intravenous drug abuse, previous trauma and soft tissue infections; however, many adult cases are idiopathic. Most NSTIs in infants are a result of secondary infection of omphalitis, balanitis, mammitis, postoperative complications, and fetal monitoring.

Presenting Symptoms and Physical Findings

Many patients with NSTI present initially to a primary care physician or dermatologist. There may be a history of soft tissue injury from an animal or insect bite, blunt or penetrating trauma, or subcutaneous injections of insulin or illicit drugs. Sometimes an inconsequential scratch or abrasion may be implicated. NSTI also occurs in the hospital setting as a postoperative complication. Distinguishing NSTI from other less severe infections is difficult but crucial since NSTI is a surgical emergency.

A majority of NSTI patients (47–94%) present with an erythematous, tender, swollen area resembling cellulitis with disproportionately severe pain at the site of involvement (2, 4–6). Other less common presenting complaints include fever, chills, weakness, confusion, and rash. The most common physical findings are listed in Table 2. Due to the myriad presenting signs and symptoms, the diagnosis is often not apparent initially. Health-care providers must be cautious when confronted with such patients. Certain findings once believed to be classic are not as common as previously thought. The presence of crepitus on physical examination or soft tissue air on plain x-ray is seen in only 37% and 57% of patients respectively (4). The absence of such "classic" findings does not rule out NSTI, so one should not be lulled into a state of complacency if they are not present (2, 4, 6). On the other hand, the presence of these findings is pathognomonic for NSTI.

As the infectious process progresses, the skin characteristically becomes more erythematous, painful and swollen, with indistinct borders. The skin develops a violaceous hue, may become necrotic with bullae formation, and eventually appears hemorrhagic and gangrenous (10). There may be involvement of more than one area, separated by islands of normal skin. Involvement of the muscle and/or nerves may lead to weakness and loss of sensory innervation.

Symptoms of NSTI are often present for several days before the patient presents. As a result of this delay, signs of advanced infection may be present. Hypotension, tachycardia, mental

TABLE 1
Pre-existing Conditions that Have Been Associated with Necrotizing Soft Tissue Infections and Presumed to Be Causes of These Types of Infections.

Pre-existing Factor	Incidence	Reference
Diabetes mellitus	21–64%	1, 2, 4, 6, 7
Chronic renal insufficiency	10%	4
Peripheral vascular disease	15–80%	2, 4–7
Acute renal failure	15%	4
Age > 60	31%	4
Intravenous drug abuse	8–67%	1–4, 6
Obesity	18–46%	1, 2, 4, 6, 7
Chronic alcoholism	12–31%	1, 2, 4
Malnutrition	18–40%	1, 2, 4–6
Steroids	12%	4
Paraplegia	3%	6
Cancer	2–12%	1, 4
Etiology		
Infections, soft tissue	11–90%	1, 5, 6
Intravenous drug abuse	27–56%	1–4, 6
Post-operative infection	3–14%	1, 6, 7
Perirectal abscess	9–15%	1, 6
Trauma	15–55%	1, 3, 6
Idiopathic	2–38%	1, 3, 6, 7
Insect bites	6–7%	3, 6

TABLE 2

Signs and Symptoms Found at the Time of Admission for Patients Presenting with Necrotizing Soft Tissue Infections.

	Frequency	Reference
Symptom		
Pain	47–94%	2, 4–6
Mental obtundation	18%	4
Sign		
Swelling	67–75%	2–4
Erythema/cellulitis	66–100%	1–7
Crepitus	12–36%	2, 4, 6
Fever > 100.5°F	32–100%	1, 2, 4, 6, 7
Skin slough/necrosis	31–47%	1–4, 7
Blistering/bullae	10–24%	3, 4, 7
Skin discoloration	18%	4
Hypotension	11%	4
Laboratory findings		
Leukocytosis (>10,000/mm^3)	49–88%	1, 2, 4, 6
Anemia	38–64%	2, 4, 6
Acidosis (<7.36)	33–35%	1, 4, 6
X-ray findings		
Soft tissue air		
Plain x-ray	17–57%	1, 2, 4, 7
CT	12%	4

obtundation, skin mottling, acute renal failure, lactic acidosis, leukocytosis, and increased cardiac output with concomitant, reduced peripheral-vascular resistance may be encountered (Table 2). Some laboratory findings common in NSTI, but by no means diagnostic, include elevated white blood cell count, glucose, lactate, BUN and creatinine levels. Anemia, hypocalcemia, hypoalbuminemia, an altered coagulation profile, and decreased oxygenation may also be present (1, 2, 4, 6). Such findings are not present in all patients but may be helpful in suggesting the diagnosis (Table 2).

Radiographic evaluation has been used primarily for patients whose diagnosis was in doubt. Plain films of the involved area may show evidence of soft tissue air (2–4, 7). This is a significant finding in any patient and needs to be addressed immediately with surgical exploration. Computed tomography (CT) and magnetic resonance imaging (MRI) have also been employed in equivocal cases and have sometimes been helpful in defining the presence and extent of infection (4, 11, 12). It cannot be overemphasized, however, that these studies are only adjuncts in the evaluation of patients with potential NSTI and should not be relied upon to exclude that diagnosis. The diagnosis is still primarily a clinical one. Most important, the extent of debridement is determined by physical findings at the time of surgery and not by CT findings.

Some authors advocate the use of fine-needle aspiration for diagnosing NSTI but this procedure has limited usefulness and can be misleading. A positive aspiration confirms infection, but a negative examination does not exclude it. If the diagnosis is suspected, it is our opinion that a more definitive procedure such as incisional biopsy or surgical exploration is indicated (3).

A more recent approach to the diagnosis of NSTI is bedside incisional biopsy down to the fascial level (13). This biopsy is immediately sent for frozen section culture and Gram stain. This analysis is far more accurate than that performed on a fine-needle aspirate. Incisional biopsy appears to be the only reasonable approach to the diagnosis other than a trip to the operating room. Punch biopsy should not be used as an alternative to scalpel incisional biopsy, since it can easily miss the pathology.

Sites of Presentation

Although NSTIs can occur anywhere on the body, they are more common in certain locations. Perineal soft tissue infections, termed Fournier's gangrene, are seen in up to 36% of cases (1, 3, 4) and the extremities are involved in 36–53% of NSTI. The trunk accounts for 18–64% of cases (1–7). The distribution reflects the particular patient population seen at each institution.

Bugs and Drugs

All tissues obtained at the time of initial surgical debridement should be subjected to aerobic and anaerobic cultures and Gram staining. Although the Gram stain has been suggested as a guide to initial antibiotic therapy of NSTI, it is of limited value given the polymicrobial etiology of most cases. Recently, two cases of Group A streptococcal (GAS) associated NSTI were reported in which GAS was identified using the standard rapid streptococcal diagnostic kit (14).

Cultures of NSTI have yielded a wide variety of pathogenic organisms in different studies (Table 3). Factors that affect bacterial isolates identified include handling of specimens at surgery, use of aerobic and anaerobic culture media, delay in plating in the laboratory and final interpretation of cultures. Other variables that determine the bacteriology of NSTI include site of infection and clinical setting. Postoperative abdominal wound infections and perineal infections may yield gastrointestinal flora.

Infection with a single pathogen occurs in 15–29% of cases and polymicrobial infections are seen in the remainder (1, 3, 4, 6). Of the latter, roughly one-half will have mixed aerobic flora, and the other half mixed aerobic and anaerobic growth (1–7). In a small number of cases (7–15%), only anaerobic bacteria are identified, and rarely no organisms are isolated (1, 2, 4).

GAS infections have received much attention recently as etiologic agents of NSTI (15–19), referred to in the lay press as "flesh-eating bacteria." In a recent study, GAS were isolated in only 16% of patients with necrotizing fasciitis (20). Of the 8 patients in whom GAS was isolated, one grew only streptococci, and in six it was accompanied in two patients each by *Staphylococcus aureus*, *Acinetobacter anitratus* and *Klebsiella pneumoniae*. There was mixed growth in the remaining patient. Another recent study identified GAS in 10 of 14 patients (71%) with necrotizing fasciitis (8). In a study of necrotizing skin infections in children, GAS was seen as a single organism in only 25% percent of cases while the remaining cases were polymicrobial (21).

An important aspect of streptococcal NSTIs is that they can occur in otherwise healthy people at any age and may cause rapid onset of shock and multiple-organ failure. They may follow minor or major trauma, injection of illicit drugs, accidental needle sticks and varicella infections in children and adults (22–25). Elderly individuals and patients with underlying medical disease are at greater risk for serious GAS infections, necrotizing fasciitis and shock (26). Necrotizing GAS infections may occur anywhere on the body, including the trunk, extremities and even the periocular area (18).

Streptococcal toxic-shock syndrome is a complication of GAS infections. It is associated with necrotizing fasciitis in 50% of cases (27). Patients present with cutaneous pain, fever, chills, muscle ache and malaise. They may develop nausea, vomiting, diarrhea, tachycardia, tachypnea, hypotension and renal failure. Cases of so-called "toxic strep syndrome" are most commonly associated with group A streptococci M1 and M3. Streptococcal pyrogenic exotoxins which cause the rash of scarlet fever are also known to act as superantigens. It has been suggested that shock may be mediated by massive release of cytokines such as tumor necrosis factor alpha and interleukin-1 beta induced by streptococcal pyrogenic exotoxin A (SPEA) and streptolysin O (SLO) (28).

Patients suspected of having NSTI should be started empirically on broad-spectrum antibiotics covering the most commonly encountered pathogens (Table 3). The most frequently advocated antibiotic regimen includes ampicillin/penicillin, gentamicin and anaerobic coverage with either metronidazole or clindamycin (1–7). Penicillin-allergic patients may be started on aztreonam or vancomycin in place of ampicillin

TABLE 3

A List of the Most Common Bacterial Isolates for Patients Presenting with Necrotizing Soft Tissue Infections.

Gram-positive organisms*	**(%)**	**Gram negative organisms***	**(%)**
Group A streptococci	18–46	*E. coli*	8–28
Enterococci	16–34	Enterobacter	2–12
Coagulase (-) Staph	15–37	Pseudomonas species	9–20
Staph. aureus	9–37	Proteus species	6–12
Staph. epidermidis	18	Serratia species	2–6
Clostridial species	5–21	Bacteroides	18–48
Mixed Gram positive	10	Mixed Gram negative	16

* References 1–7.

or penicillin. There is experimental evidence suggesting that clindamycin may be superior to penicillin in overwhelming streptococcal infections. Penicillin may be less effective due to an "inoculum effect" of large numbers of slower-growing organisms with decreased expression of certain penicillin-binding proteins (27). Clindamycin, which works by inhibiting protein synthesis, is not subject to such effects; moreover, it suppresses the production of certain bacterial toxins. It may be given in conjunction with penicillin.

Subsequent antibiotic management is guided by the sensitivities of the organisms identified from intraoperative cultures. Incorrect handling of specimens may result in falsely negative anaerobic cultures, so antibiotic coverage of anaerobic organisms is still advisable. Antibiotic coverage should be continued until the infection is under control and for at least 48 hours after the temperature and white blood cell count have returned to normal.

Treatment

Once the diagnosis of NSTI is made, treatment should be instituted promptly. Resuscitation, based on the clinical state of the patient, includes aggressive fluid replacement to manage acute renal failure from ongoing sepsis and shock. Intravenous antibiotics are given and appropriate measures are taken to maintain cardiac output and pulmonary stability. Urine output should be monitored via an indwelling urinary catheter.

The patient should be brought to the operating room without unnecessary delay and undergo aggressive and extensive operative debridement by a team of general and plastic surgeons (1–7). The skin, soft tissue and muscle should be debrided until there is no further evidence of infected tissue, based solely on the findings at surgery (Figs. 3, 4). The first operative debridement is the most important one for the survival of the patient. It is preferable to remove more tissue than necessary than to leave any actively infected or necrotic tissue. The patient should then be returned to the operating room daily to confirm that there has been no extension of the infectious process and to debride any skin and soft tissue edges that have become desiccated. The total number of trips to the operating room is based on the condition of the wound and whether the infection has been adequately controlled. Once the infection is controlled, daily dressings can be done at the bedside, with sedation. Our approach is to cover soft tissues with split-thickness skin grafts once the infection has been eradicated. Only rarely are more extensive procedures needed in the acute setting. For our patient, this was begun on the third visit to the operating room and was completed by the 15th day of hospitalization. Prompt closure of wounds is important to eliminate a portal of entry for continued bacterial infection, to prevent ongoing serum loss, and to allow for early rehabilitation. After the patient has recovered from the acute process, the plastic surgeon may perform tissue transfer to close persistent defects or repair areas that need more than skin coverage.

The role of amputation in controlling NSTI is controversial. If infection can only be eradicated by amputation, it should be done promptly and without hesitation. Controversy also exists concerning the role of colostomy in patients with perineal wounds. If there is regular fecal contamination of the wounds, colostomy should be performed. Because NSTI can involve the abdominal wall in the usual sites of colostomy placement, this procedure should be performed only after control of the infection and in an uninvolved area.

While some authors have advocated the use of hyperbaric oxygen in the treatment of NSTI, in addition to operative debridement, its usefulness is controversial (4, 29, 30). It has never been shown to improve survival rates when compared to standard operative and supportive therapy (4, 29, 30). Moreover, few institutions have facilities for hyperbaric treatment and patients are often too ill to be transported there for treatments.

Postoperative Course and Complications

Patients with NSTI can develop multiple-organ-system failure and should be managed in an ICU. Respiratory insufficiency is common and prolonged mechanical ventilation and tracheostomy are often required. Renal failure is usually transient and can be managed medically. Either intermittent hemodialysis or continuous arterio-venous or veno-venous hemofiltration may be used, as was the case in our patient, to ameliorate the problems associated with acute renal failure. Renal function usually improves once infection has been controlled. Blood pressure support is often required in the immediate postoperative setting due to septic shock. Central venous and cardiac pressures are routinely monitored with a Swan-Ganz catheter and adrenergic agents are used to maintain blood pressure and cardiac output. Hemodynamic parameters usually improve with control of infection.

When the patient has completely recovered from the acute effects of NSTI, rehabilitation should be instituted as soon as possible, to ensure complete functional recovery. The particular therapy will depend on the area affected, the amount of tissue removed, the muscles involved and the duration of the hospital stay. Physical therapy can often be started in the ICU and then be continued when the patient is transferred to the surgical floor. If long-term reconditioning is necessary, the patient should be transferred to a skilled rehabilitation facility prior to returning home.

Prognostic Factors for Mortality

The reported mortality rate for NSTI varies from 6% to 33% (1–7). The relative importance of some prognostic factors has been investigated (Table 4), but they are only of academic interest since the physician has little or no control over most of them.

Elliott et al. demonstrated that a combination of factors is more predictive of outcome than any individual factor (4). In their study, diabetes mellitus did not predict outcome, but when combined with peripheral vascular disease, renal failure, and age greater than 60, it was associated with a significant increase in mortality (4). Elliott et al. also showed that elevated serum creatinine, blood lactate, and organ failure at the time of admission predicted a poor outcome (4). The white blood cell count, serum glucose level, and platelet counts were not associated with an unfavorable prognosis (4). While the site of infection has been suggested to impact on survival, it is difficult to ascertain because studies have had different distributions of involvement. Despite this, truncal and perineal infections are thought to have higher mortalities (4). Delay in diagnosis and surgical management are frequently implicated as important predictors of increased mortality (1–6). Inasmuch as patients often delay in seeking medical attention, the physician has limited control over mortality rates. When the patient does finally present, the diagnosis is often missed. Sometimes, the diagnosis of NSTI is not entertained until the situation worsens. Delay in diagnosis allows more time for the infection to advance and this adversely affects outcome (1–6). An increased index of suspicion for NSTI may hasten the diagnosis and treatment, thus improving the prognosis.

The major factor that physicians can control is the extent of debridement, and this appears to be the most important determinant of survival (1–7). Inadequate surgical debridement at the initial operative procedure results in adverse outcomes, with disease progression, multi-system failure and death.

TABLE 4

Factors that Have Been Evaluated to Determine the Mortality Rate in Patients with Necrotizing Soft Tissue Infections.

No effect on mortality	Increases mortality
Race	Cardiac disease
Blood glucose	Presence of malignancy
Platelet count	Malnutrition
Hepatic disease	Intravenous drug abuse
HIV	Renal failure
Albumin level	Peripheral vascular disease
Myonecrosis	Elevated serum lactate
Abnormal vital signs	Obesity
Pulmonary disease	Body surface involved
	Diabetes mellitus
	Age > 60
	Delay in operative debridement
	Limited incision and drainage

Conclusions

NSTIs are relatively uncommon infections that often present for medical attention late in their course. The diagnosis is often missed at initial presentation, allowing further progression of the infectious process. Patients most commonly present with pain at a soft tissue site, with erythema and tenderness. The diagnosis is made clinically based on the visual findings in the infected area and by a high index of suspicion on the part of the clinician. Laboratory tests and plain x-rays may support the diagnosis but are frequently normal despite ongoing infection. CT and MRI are sometimes useful, but the critical condition of the patient often precludes their use. They should not be relied upon to exclude the diagnosis of NSTI if the diagnosis is suggested. Once the diagnosis has been made, the patient is stabilized and taken to the operating room for debridement. Surgical debridement should be performed daily until the acute infection has been controlled. Outcomes are based on the promptness of diagnosis, surgical treatment, and the management of postoperative complications. A multi-disciplinary team of health-care personnel, including general surgeons, plastic surgeons, infectious disease specialists, intensivists, rehabilitation staff and nursing staff, are needed to provide the extensive resources and time it takes for patient recovery.

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Update on Panniculitis

Robert G. Phelps, M.D., and Toru Shoji, M.D., Ph.D.

Abstract

There is considerable confusion regarding the pathogenesis, nosology and treatment of panniculitis. This paper examines newer concepts in five types of panniculitis: i.e., histiocytic cytophagic panniculitis, erythema induratum, lipodermatosclerosis, pancreatic panniculitis and alpha-1-antitrypsin deficiency panniculitis. Recent developments in etiology, pathogenesis, molecular techniques, and therapy are discussed.

Key Words: Panniculitis, lymphoma, cytophagic, alpha-1-antitrypsin, pancreatitis.

Panniculitis has been observed in a number of clinical entities. These include erythema nodosum, erythema induratum, Weber-Christian panniculitis, pancreatic fat necrosis, lupus panniculitis, as well as others. Histologically, inflammation may predominate in the septae of the panniculus or within fat lobules, and the pattern of inflammation can often be useful in distinguishing these entities. On the other hand, the precise pathology of many so-called "well-defined" panniculitides can be confusing, since the histology depends on the stage of the lesion, which may evolve from day to day. The general pathology of panniculitis has previously been reviewed (1, 2). We will present material on five uncommon types of panniculitis in which significant advances have been made in the past ten years.

Histiocytic Cytophagic Panniculitis

Originally, histiocytic cytophagic panniculitis (HCP) was classified as a systemic histiocytosis. HCP, first described by Winklemann and associates (3, 4), has a characteristic clinical presentation. Patients develop large, ecchymotic, subcutaneous nodules that frequently become ulcerated. Systemic manifestations such as fever and malaise are common, as are anemia, leukopenia, thrombocytopenia, elevated hepatocellular enzymes, and a severe coagulopathy; often there is disseminated intravascular coagulation. While many patients with HCP suffer from relatively indolent variants of the disease, many others die as the result of massive visceral hemorrhage or organ system failure (5). Pettersson et al. reported that chemotherapy usually has only limited efficacy (6). However, a recent report by Ito et al. suggests that CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) therapy combined with cyclosporin A may be useful (7).

The pathology of HCP is quite distinctive (3, 4). Characteristically, there is prominent infiltration by histiocytes within the subcutis. These histiocytes, which phagocytize erythrocytes and other cells, have been referred to as "beanbag" cells. Peripherally, there are small lymphocytes that are cytologically benign. Similar infiltration affects other areas as well, including bone marrow, lymph nodes and other tissue of the reticuloendothelial system.

Three recent developments have changed our understanding of this entity. The first was the realization that certain cases of so-called systemic Weber-Christian panniculitis with visceral involvement actually represent HCP.

Weber-Christian panniculitis was originally described in the 1920s as a poorly defined, local, non-suppurative condition involving the subcutaneous fat. Other cases of Weber-Christian panniculitis were reported in which there was suppuration and/or visceral involvement. Ultimately, the condition was considered to progress through three stages: the first was characterized by suppuration; "foam cells" are prominent in the second; and fibrosis develops in the third. The second stage of Weber-Christian panniculitis was alleged to be the most diagnostic. It is now clear that: (a) the histology of Weber-Christian disease is not as specific as was previously thought and (b) many cases of "systemic" Weber-Christian disease, upon sub-

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sequent review, have been proven to represent other types of panniculitis. It is now also apparent that those cases with bone marrow and serosal involvement demonstrate cytophagocytosis and therefore should be reclassified as cytophagic panniculitis (8, 9).

The second development that changed our understanding of HCP was the realization that there is a clinical and histologic overlap of some cases of HCP with subcutaneous panniculitic T-cell lymphoma. In panniculitic T-cell lymphoma, cytologically atypical lymphocytes are found adjacent to benign-appearing histiocytes which have engulfed a variety of other cell types (10). This condition has a clinical course and prognosis similar to that of cytophagic panniculitis (11). We and others have demonstrated that cytophagic panniculitis often shows a concomitant lymphoma or molecular genetic evidence of a clonal process (12), and has an adjacent infiltrate of T cells. The histiocytes in both conditions seem to have a normal immunohistochemical profile and appear cytologically benign. It is tempting to speculate that cytophagic panniculitis and subcutaneous T-cell lymphoma represent variants of the same disease process, one in which the lymphocytes are atypical and clearly malignant, the other in which lymphocytes are also most likely malignant but cytologically benign appearing. In both variants, these lymphocytes presumably produce cytokines that induce benign-appearing histiocytes to engulf surrounding inflammatory cells (12).

The third important recent development that has affected the concept of HCP is evidence of the presence of concomitant Epstein-Barr Virus (EBV) infection. EBV-encoded RNAs have been found in infiltrating T cells in both HCP and panniculitic T-cell lymphoma (13–16). For unknown reasons, EBV involvement seems to occur more commonly in cases in Asia than in the United States. American cases have mostly been EBV negative, except for those in which there were angiodestructive foci in which medium-sized blood vessels were infiltrated and destroyed by atypical lymphocytes.

The implication of these three developments is clear. If a patient presents with a panniculitis with prominent skin involvement and systemic signs and symptoms, a comprehensive diagnostic work-up is mandatory. It is important that the initial skin biopsy be step-sectioned to look for evidence of cytophagocytosis, because this feature, which is often focal and minimal, can easily be missed. Second, if there is evidence of extracutaneous (e.g., lymph node or bone marrow) involvement, tissue biopsies should be obtained from these sites. Tissue biopsies can detect cytophagic changes that may not have been detected on skin biopsy. Third, if there is a suggestion of recent viral or infectious illness, the patient should be evaluated for EBV infection. Once the diagnosis of HCP is established with complete certainty by the histological exclusion of other types of panniculitis, systemic chemotherapy is advisable.

Erythema Induratum

Erythema induratum is a type of panniculitis that has, in a sense, come full circle. When first described by Bazin in 1861 as "erythème induré des scrofuleux" (17), it was thought to be a tuberculid, i.e., a skin eruption occurring in patients as a hypersensitivity reaction to concomitant tuberculosis. At that time, the concept of hypersensitivity to tuberculosis seemed reasonable, given the high prevalence of tuberculosis in the population and the presence on pathologic section of features typical of tuberculosis, e.g., "caseous" necrosis of fat (18). Moreover, there were cases, albeit very rare, in which the organism was isolated from involved tissue.

However, there are many patients with identical dermatologic presentations and similar pathologic findings in whom tuberculous infection cannot be identified. This occurs most often in women who have no concurrent systemic infection and in whom the circulation in the legs is "sluggish." The pathology is similar, though not identical. This variant of erythema induratum, allegedly due to vascular disturbance, was first described by Galloway and later by Whitfield (19), and has been referred to as nodular vasculitis. As tuberculosis became less common, its association with erythema induratum became less tenable (1).

Recently, however, two events have turned back the clock on the concept of erythema induratum: (a) the re-emergence of tuberculosis with the HIV pandemic and the occurrence of multi-drug-resistant strains (20) and (b) the development of polymerase chain reaction (PCR) technology (21–23). The resurgence of tuberculosis has been accompanied by an increased incidence of erythema induratum. We have recently reported two cases in which the clinical diagnosis of erythema induratum was essential to the diagnosis of tuberculosis infection, which had not been suspected clinically (20). In one case, a 21-year-old woman with vague constitutional symptoms developed an ulcerating panniculitis. Repeated pathologic examinations failed to disclose an etiology for the panniculitis but suggested erythema induratum. Eventually, mediastinal lymph node biopsy was performed and unequivocally established the diagnosis of tuberculosis. The second patient, who presented with lower extremity ulcers diagnosed as erythema induratum (18), was found to have pulmonary tuberculosis.

PCR technology, which allows the amplification of trace quantities of DNA in tissue, has revolutionized the study of disease entities thought to be related to infectious organisms. In most cases of erythema induratum, even though no mycobacteria can be demonstrated by culture, special stains, or animal inoculation experiments, the clinical association with tuberculosis is undeniable. The PCR technique is able to detect DNA from *Mycobacterium tuberculosis* in fresh clinical specimens and even in paraffin-embedded tissue that has been stored for long periods of time. Penneys et al. (24), using a probe for mycobacteria, looked at five specimens from lesions known to be tuberculids and detected DNA from tuberculosis in virtually all of the lesions. Baselga et al. (22), using probes for mycobacteria in a nested PCR assay, looked at cases of erythema induratum and found that DNA from *M. tuberculosis* was present in 75% of the cases.

These data suggest that tuberculosis might be the cause of many cases of erythema induratum and that antituberculosis therapy ought to be helpful. Paradoxically, some studies have failed to show any correlation between response to antituberculosis drugs and positive PCR results, whereas other treatments, e.g., systemic steroids, have been effective. This is especially significant, since corticosteroids can cause reactivation of tuberculosis and are usually avoided unless the patient is on antituberculosis therapy.

Lipodermatosclerosis

For many years it has been apparent that patients with stasis dermatitis, an ostensibly epidermal and superficial dermal process, often develop changes in the deeper dermis and subcutis. Damage to superficial capillaries occurs early on in this condition. And the vascular fragility causes repeated hemorrhage into the dermis, which manifests clinically as reddish-brown discoloration of the legs from hemosiderin deposition. There is persistent edema, superficial and then deep fibrosis, and ultimately, in some cases, ulceration. The deep fibrosis results in a constricting panniculitis.

The clinical appearance of this disease process is quite remarkable. The legs above the ankles start to taper suddenly, forming a constricting band resembling an inverted coke bottle. In addition, there is brownish-red pigmentation and induration. This combination of lesions in the dermis and subcutis is called lipodermatosclerosis.

The pathology of this condition is quite variable (25, 26). In the superficial portions of the biopsy, the changes are typical of venous stasis. Thick-walled capillaries, surrounded by fibrin, often extend deeply. Siderophages (macrophages that have ingested iron) are present around capillaries, and fibrosis is noted.

The changes may extend into the fat. Early on, there is lobular as well as septal panniculitis, both mediated by lymphocytes. Later on, ischemic necrosis of fat becomes evident. Multiple small and large cystic spaces form and coalesce. These cystic spaces are frequently lined with thick, eosinophilic, PAS-positive material that is believed to represent condensation of lipocyte membranes. The membranes are arrayed in complex arabesque patterns that give this panniculitis its characteristic appearance (Fig. 1) (27, 28). Because of this pattern, lipodermatosclerosis has had many names, including membranous lipodystrophy and lipomembranous fat necrosis.

Although these changes are alleged to be very characteristic, many have called their

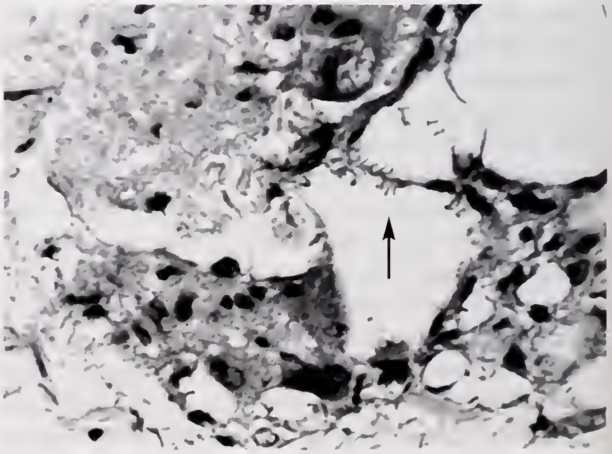

Fig. 1. Characteristic membranocystic change seen in lipodermatosclerosis. A multinucleated giant cell surrounds a convoluted cell membrane showing the so-called "arabesque" pattern (arrow) (hematoxylin and eosin, 100x).

specificity into question. The same change previously had been described in a genetic disease, membranous lipodystrophy, and Snow et al. (29) described almost identical changes in cases with classic clinical and histologic features of morphea. However, in that study there was microcystic change in the fat.

Therapy for lipodermatosclerosis focuses on the usual treatments for venous stasis, including bed rest, leg elevation, and stocking compression. In view of the intimate association with fibrin cuffs and capillary leakage, some have advocated fibrinolytic agents such as the anabolic steroid, stanozolol (30).

Pancreatic Panniculitis

Pancreatic panniculitis is a rare condition in which necrosis of fat occurs in subcutaneous tissue and elsewhere in the setting of pancreatic disease (31–35). The distinctive clinical presentation and pathognomonic histopathologic findings may be the presenting features of underlying pancreatic pathology.

Pancreatic panniculitis usually occurs in association with pancreatitis or pancreatic carcinoma, both of which have a male predominance (3.5:1). Interestingly, pancreatic acinar carcinoma, which accounts for only 10% of all pancreatic carcinoma, is associated with 84% of pancreatic panniculitis cases (34). Patients present with tender, erythematous, fluctuant nodules that may drain an oily substance. An associated arthritis and/or polyserositis (32) may be present as well. Because of the tenderness and arthritis, pancreatic panniculitis is often mistaken for erythema nodosum.

The histopathology of pancreatic panniculitis in early stages characteristically includes lobular fat necrosis with ghost-like fat cells and a surrounding polymorphous infiltrate of neutrophils, lymphocytes, macrophages, and foreign-body giant cells (Fig. 2). There may be foci of calcification and focal hemorrhage. A report of a biopsy of a 2-day-old lesion purporting to show septal panniculitis, a feature more characteristic of erythema nodosum (36), raised the possibility that pancreatic panniculitis may evolve from an early septal reaction to a fully developed lobular panniculitis. In older lesions, the histopathology can show a nonspecific fibrosing reaction with foamy macrophages and hemosiderin deposition. Birefringent, saponified, fatty-acid crystalline structures have been found in pancreatic fat necrosis from the mesentery (37) and in the associated arthritis (38), but not in cutaneous lesions.

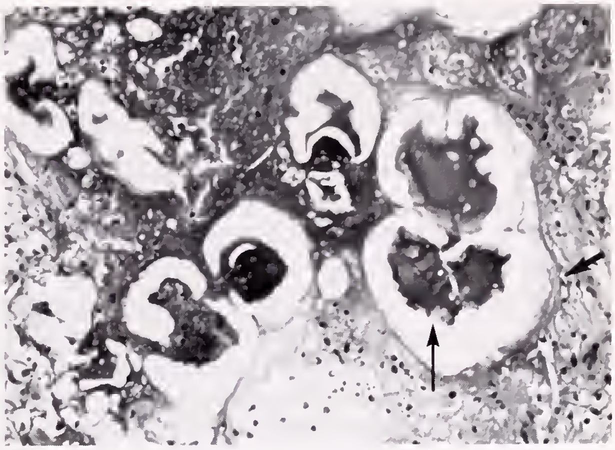

Fig. 2. Necrotic lipocytes (thin arrow) surrounded by a thin rim of calcium (wide arrow) seen in pancreatic panniculitis (hematoxylin and eosin, 100x).

Pancreatic panniculitis is caused primarily by lipase, phospholipase, trypsin, and amylase. The mechanism of activation of precursor pancreatic enzymes into activated forms is not clear. It is tempting to speculate that vascular damage from increased levels of circulating pancreatic enzymes might increase vascular permeability, thereby allowing the enzymes to enter fat lobules and cause necrosis. Therapy should be directed to the primary disease, though symptomatic treatment with support hose and leg elevation may be helpful.

Alpha-1-Antitrypsin Deficiency Panniculitis

Alpha-1-antitrypsin (alpha-1 AT) is a proteinase inhibitor (pi) that is produced in the liver and accounts for much of the proteolytic inhibitory activity in the blood. It inhibits many other serine proteinases in addition to trypsin. Its serum concentration is determined by the inheritance of autosomal co-dominant alleles, with M, S, and Z the most abundant. PiZ homozygotes have only 10–20% of the normal serum concentration of the proteinase inhibitor and have an increased risk for the development of pulmonary emphysema. Some 10–20% of the Z homozygotes develop neonatal hepatitis, with or without cirrhosis. SZ heterozygotes have one-third of the normal inhibitor level and a relatively low risk of developing emphysema, while MZ heterozygotes have a moderate risk (39). In addition to the well-recognized association of pulmonary emphysema, neonatal hepatitis and cirrhosis with alpha-1 AT deficiency, distinctive ulcerating lobular panniculitis may also occur. Since the original description by Warter et al. (40), numerous cases of ulcerative lobular panniculitis have been reported (41–44).

Alpha-1 AT deficiency panniculitis is characterized clinically by recurrent, tender, erythematous, subcutaneous ulcerating nodules usually seen on the trunk and extremities. It is occasionally associated with a history of previous trauma. The serum alpha-1 AT level is significantly decreased. Most cases are of the PiZZ phenotype (45–49), although other types have been reported (50, 51).

Biopsy of well-formed lesions shows a lobular panniculitis with mixed infiltrate of neutrophils and histiocytes. Secondary leukocytoclastic vasculitis may be seen in areas of necrosis. A direct immunofluorescence study reported complement (C3) and/or IgM in blood vessels of the panniculus or dermis (52). In early-stage disease, a sprinkling of neutrophils between collagen bundles in the reticular dermis may be the only finding (53). Therapies that appear to be of greatest benefit include dapsone as well as alpha-1-proteinase inhibitor replacement (54).

Summary

We have discussed recent advances in the diagnosis, pathogenesis and treatment of five different types of panniculitis. It is clear, even from this limited review, that many of the entities are difficult to diagnose. Yet appropriate diagnostic tests, along with an adequate biopsy, notwithstanding the histologic overlap, should provide some help in treating these conditions.

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Current Therapy of Pemphigus Vulgaris

Michael J. Fellner, M.D., and Allen N. Sapadin, M.D.

Abstract

Pemphigus vulgaris (PV) is a potentially fatal autoimmune blistering disease of the skin and mucous membranes, characterized by flaccid bullae that rupture and leave erosions. Its treatment is challenging. Although the use of systemic corticosteroids remains the cornerstone of effective therapeutic regimens for PV, their prolonged administration may lead to serious side effects. It is therefore necessary, for many patients, to add immunosuppressive agents or use immunomodulatory procedures to achieve remission. This paper will summarize the treatments available for PV, while focusing on the most recently available therapeutic options.

Key Words: Pemphigus vulgaris, therapy.

Introduction

The pemphigus group of diseases is characterized by potentially life-threatening blistering of the skin and mucous membranes. An autoimmune process, directed against keratinocyte desmosomal cadherins, interferes with the adhesive function of these molecules. This results in separation between keratinocytes, which in turn leads to the clinical manifestation of blistering.

There are three major types of pemphigus: pemphigus foliaceus (PF), pemphigus vulgaris (PV), and paraneoplastic pemphigus (PNP). In PF, scaly crusted erosions evolve from flaccid blisters. The lesions may be localized and have a seborrheic distribution, or may become generalized. Mucous membrane involvement is rare. Patients with pemphigus erythematosus, a variant of PF, have some serologic findings suggestive of systemic lupus erythematosus, in particular, antinuclear antibodies.

In PNP, a severe mucocutaneous blistering eruption develops in the context of an underlying neoplasm. Approximately 70% of the patients will have underlying non-Hodgkin's lymphoma or chronic lymphocytic leukemia, although other lymphoproliferative disorders have been described. Erosions of the lips with hemorrhagic crusting are the most constant clinical finding, and may resemble Stevens-Johnson syndrome. The disease is usually refractory to treatment and the prognosis is grave. Combination therapy with prednisone and cyclosporine may prolong survival for some patients.

PV is the most common form of pemphigus. Its incidence is 0.1–0.5 per 100,000 in the U.S. population, but higher among Jewish people (1). Men and women are equally affected, and the mean age of onset is 50–60 years. Clinically, PV is characterized by flaccid bullae that subsequently rupture and leave erosions. The blisters may occur anywhere on the skin surface, but intact blisters may be sparse. Involvement of the oral mucosa is common; it is the site of onset in more than 50% of patients. Intact bullae are uncommon in the mouth, and the painful erosions of PV are often misdiagnosed as herpes simplex virus infection. Pemphigus vegetans is a variant of PV, in which vegetating lesions are seen, often in intertriginous areas.

Routine histopathologic examination reveals a suprabasilar blister, acantholysis (separation between keratinocytes), and a mild, superficial, dermal inflammatory infiltrate. Direct immunofluorescence (using the patient's perilesional skin as a substrate) reveals antibody (IgG) deposition in the intercellular spaces of the keratinocytes. Indirect immunofluorescence (using the patient's serum on monkey esophagus substrate) is positive in more than 90% of patients with active disease (2). Desmoglein 3, a 130 kDa component of the desmosome, is the target antigen in this disease. Deletion of the desmoglein-3 gene in mice re-

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sults in a phenotype consistent with PV, including oral mucosal and skin erosions (3).

The severity and natural history of PV are variable. Many published reports group PV and PF patients together. This makes it difficult to analyze the specific data on PV. In the era before corticosteroid therapy, the vast majority of patients with the pemphigus group of disorders died from their disease. Changes in therapy over the past century have reduced the mortality from this disease to less than 10% and many of these deaths are now iatrogenic in nature. This dramatic decline in mortality is due primarily to the marked improvement in therapeutic options, but also to earlier diagnosis and initiation of therapy.

The current treatment options for PV are listed in Table 1. This paper will review these conventional and new treatments, with an emphasis on the most recent literature.

Corticosteroid Treatment

Before the 1950s the majority of patients with pemphigus died, usually from overwhelming sepsis, within one year of the onset of their disease. A clear and rapid fall in the mortality rate occurred after the introduction of corticosteroids in the 1950s (4).

Topical and Intralesional Corticosteroids

Both topical and intralesional corticosteroids have been used in the treatment of PV, but they are more effective in the treatment of PF and bullous pemphigoid. Dumas et al. (5) described 7 pemphigus patients, 3 of whom were treated with clobetasol propionate 0.05% cream as monotherapy for their mild PV. PV was defined as "mild" if fewer than 10 new bullae appeared per week and if the circulating pemphigus antibody titer was ≤ 1:320. The cream was applied twice a day for at least 15 days, then tapered. Lesions were controlled in only 1 of the 3 PV patients.

Triamcinolone acetonide, diluted to 5 – 10 mg/mL, may be used for intralesional injections of cutaneous lesions. A higher concentration, 10 – 20 mg/mL, is recommended for intraoral lesions (6). Multiple injections may be necessary for large lesions. The injections should be administered at weekly or biweekly intervals until complete resolution of the lesions is achieved. The injections are useful for the treatment of PV of mild severity, for the treatment of resistant lesions, for vaginal lesions (7) and to treat new lesions in patients whose systemic medication is being tapered.

TABLE 1
Treatment of Pemphigus Vulgaris.

1. **Corticosteroids**
    - Topical and intralesional corticosteroids
    - Oral corticosteroids
    - Pulse therapy

2. **Immunosuppressive Drugs**
    - Azathioprine
    - Cyclophosphamide
    - Cyclosporine
    - Mycophenolate mofetil
    - Chlorambucil
    - Methotrexate

3. **Anti-inflammatory Drugs**
    - Gold
    - Dapsone
    - Nicotinamide and tetracycline

4. **Immunomodulatory Procedures**
    - Plasmapheresis
    - Extracorporeal photopheresis
    - Intravenous immunoglobulin

Systemic Corticosteroids

Systemic corticosteroids are the most useful drugs in the treatment of pemphigus vulgaris and continue to be the mainstay of therapy for this disease. Their use rapidly induces remission in the majority of patients (8 – 10).

Oral corticosteroids. The oral route of administration of corticosteroids is the one most preferred, and prednisone is the medication most frequently used. Various treatment strategies have been reviewed in detail (6, 11), but there are no controlled studies to evaluate their relative efficacy or safety profiles. For severe disease, the Bystryn regimen (6) recommends 80 mg of prednisone administered daily. If necessary, the dose is increased by 50% every 4 – 7 days until control is achieved, as demonstrated by the absence of new lesions and the disappearance of itching. This dose is maintained until there is 80 – 90% clearance of lesions. Reduction of the dose by 50% is recommended at two-week intervals.

Moderately severe pemphigus is managed with 60 – 80 mg/day of prednisone. Mild disease is treated with a trial of topical corticosteroids, followed by low-dose (20 mg/day) oral steroids (11). When the daily dose of prednisone exceeds 120 mg, it is given in 2 divided doses. If the total daily dose exceeds 240 mg, alternative options are considered. About 50%

of the patients receiving this treatment regimen are ultimately able to discontinue all therapy (12). An additional one third of the patients require daily maintenance therapy with a prednisone requirement of less than 10 mg or with an additional medication listed in Table 1. Larger maintenance doses will be required by 10 – 20% of the patients.

Pulse corticosteroid therapy. "Pulse corticosteroid treatment" refers to the intravenous administration of 1 gram/day of methylprednisolone, or its equivalent, over a period of 1 – 3 hours, for several consecutive days. The goal of this approach is to quickly achieve the immunosuppressive effects of glucocorticoids, while avoiding the long-term side effects associated with the oral route of administration. It is well tolerated in young and otherwise healthy patients, but may result in serious complications in those suffering from chronic disease. These include severe electrolyte imbalances, hypertension, pancreatitis, seizures, and cardiac arrhythmias (13).

A retrospective review of outcomes in a group of PV patients treated with (n=9) and without (n=6) pulse glucocorticoids indicates long-lasting benefits for the patients treated with pulse therapy (14). All patients in both groups received treatment with azathioprine, cyclophosphamide, or methotrexate. Some of the patients also received dapsone or gold. The difference in initial disease severity was not statistically significant in the two groups.

Six of the 9 patients treated with pulse therapy were classified as responders, patients whose lesions improved during pulse therapy and continued to improve afterward. Four of these patients discontinued all therapy and achieved remission. None of the 6 control patients achieved long-term remission. Based on this study, pulse corticosteroid therapy appears to be a promising option for those patients with severe PV who do not rapidly respond to conventional therapy.

Combination Therapy

Therapy which combines corticosteroids and additional medications to control severe PV is utilized to minimize the adverse effects of prolonged steroid use. Combination therapy is currently gaining popularity even as the initial treatment of PV. Bystryn (6) advocates the use of adjuvants only if serious adverse effects of corticosteroids appear, relative contraindications to their use exist, or they cannot be tapered because of repeated exacerbations of disease activity.

Immunosuppressive Drugs

Azathioprine

In 1973 Roenigk and Deodhar (15) described the successful use of azathioprine (50 – 250 mg/day) for the treatment of early PV in ten patients. Seven of these patients had never received corticosteroids or had had them completely withdrawn. Since the onset of action of azathioprine is 3 – 5 weeks, the authors cautioned that monotherapy with this agent was not the treatment of choice for the severe, generalized form of PV.

A 1987 study involving 29 patients with severe PV concluded that the combination of corticosteroid and azathioprine was successful (16). In that report 45% of the patients achieved remission. (Two patients died.) The use of azathioprine allowed for a significant reduction in the dosage and side effects of corticosteroids.

Reohr and associates treated two sisters who had PV with a combined schedule of azathioprine and steroid (17). One patient began with combination therapy of prednisone 80 mg daily plus azathioprine 150 mg daily. The second patient had a complete remission while on prednisolone (150 mg daily) monotherapy. Azathioprine (100 mg daily) was then added in order to facilitate tapering of the steroid. Both patients achieved a good result. Ouahes et al. (7) treated three PV patients with initial combination therapy of prednisone (80 – 180 mg daily) and azathioprine (100 mg daily). The steroids were subsequently tapered with good responses.

Cyclophosphamide

Cyclophosphamide is an alkylating agent with cytotoxic and immunosuppressive activities. Adverse effects include myelosuppression, alopecia, hemorrhagic cystitis, and gonadal damage (18). Carcinogenic effects include the development of bladder carcinoma, non-Hodgkin's lymphoma and squamous cell carcinoma of the skin. The indications for the use of cyclophosphamide in the treatment of PV include: (1) patients who do not tolerate large maintenance doses of corticosteroids because of the development of steroid-related complications; and (2) patients in whom steroids alone fail to control the disease.

Although use of cyclophosphamide as monotherapy was found to be ineffective (19), the addition of cyclophosphamide to prednisone often results in satisfactory control of the disease and/or permits a reduction in the prednisone dose. In 1978 Fellner et al. (20) described the use of cyclophosphamide in combination with prednisone as the initial treatment of 5 patients with PV. During a one-to-four-year follow-up period, all 5 patients remained free of lesions. Four of these 5 patients required no further medication.

The use of pulse intravenous cyclophosphamide may decrease adverse effects and risk of malignancy associated with the oral administration of this drug (21), while maintaining or improving efficacy. In 1988 Pasricha et al. (22) reported remission in 60 of 79 patients treated with intermittent, intravenous, high-dose dexamethasone and cyclophosphamide coupled with 50 mg/day of oral cyclophosphamide administered between the pulses. Intravenous dexamethasone and cyclophosphamide were given on day 1 of the pulse, while intravenous dexamethasone without cyclophosphamide was administered on days 2 and 3. The pulses were repeated every 2–4 weeks. Mortality was 3%. Complete remission was observed in 25 of 67 (37%) patients who were available for follow-up study. Partial remission was seen in an additional 52% of the patients. Of these, 25 received maintenance therapy with oral cyclophosphamide and 10 were still receiving intravenous pulse therapy. The authors later reported that, without further treatment, the disease in 5 of these patients did not recur during the subsequent 2–7 years (23).

More recently, Fleischli et al. (24) reported an uncontrolled study in which nine patients with severe or previously recalcitrant pemphigus were treated with pulse intravenous cyclophosphamide. The monthly pulses were initially administered at a dose of 0.5–1.0 g/m^2 of body surface area. The cyclophosphamide was increased by 100–250 mg per dose if the white blood cell count did not fall by more than 20 x 10^9/L at the 2-week nadir. All patients were treated concurrently with oral administration of prednisone (dosage adjusted for disease severity) and a daily dose of 50 mg of cyclophosphamide.

Seven of the nine patients had PV. Four of these seven patients had an "excellent" response to therapy, after which their prednisone requirement decreased to the range of 10–20 mg/day or was discontinued entirely (one patient). The duration of the follow-up period for these four patients ranged from 2–7 years.

Most recently Hayag et al. (25) described the successful use of immunoablative, high-dose cyclophosphamide without stem cell rescue in a patient with severe PV refractory to multiple therapies. This procedure, previously described for refractory cases of aplastic anemia, systemic lupus erythematosus, and paraneoplastic pemphigus, involves the intravenous administration of 50 mg/kg of cyclophosphamide for 4 days. Four months after the treatment, the patient's skin and oral lesions had completely healed and his pemphigus titers had decreased to zero. He is presently on no medications and his skin remains clear of lesions.

Cyclosporine

The mechanisms of action, adverse effects and monitoring recommendations for cyclosporine (CSP) have been reviewed (26). Barthelemy et al. (27) treated 9 PV patients with 6–8 mg/kg of CSP, including 4 patients in whom it was used as monotherapy. Of those 4, only 1 had a remission which lasted only 2 months after CSP had been discontinued. After failing CSP monotherapy, the remaining 3 patients in this group received combination therapy with prednisone. In 2 of these patients, the lesions cleared with the addition of 10 mg per day of prednisone.

Four of the 9 patients who were studied had not responded to steroid treatment. Within 3 weeks of the addition of cyclosporine to their regimen, the lesions had resolved. However, only 1 of these 4 patients remained clear after discontinuation of CSP.

Lapidoth et al. (28) studied 16 hospitalized patients with PV who were treated with prednisone and CSP. A historical control group consisted of 15 patients who received prednisone at an initial dose of 120 mg/day. This was decreased according to clinical response. There was a decreased time to new blister formation in the group treated with combination therapy (mean 11.1 vs. 20.5 days). Hospital stay in the treatment group was shorter (mean 32.6 vs. 50.7 days in the control group). The mean total cumulative prednisone dosage during hospitalization and follow-up was about one third less for the treatment group.

CSP was successfully administered as monotherapy in two siblings with severe PV (29). A good response was seen in both without any major side effects. The patients had been in remission for more than 20 months after discontinuation of the CSP.

More recently, Mobini et al. (30) described six patients with severe PV, including skin and oral disease, who were unresponsive to prolonged high-dose systemic corticosteroids. Subsequent therapies included azathioprine, cyclophosphamide, dapsone, gold, and methotrexate. Three patients had a major recurrence when their dosage of azathioprine was reduced. They were then treated with cyclophosphamide. Its discontinuation was necessary because of severe side effects. Dapsone, gold and methotrexate were used without success.

CSP starting doses were 1 – 3 mg/kg daily. The oral dose was adjusted over a 4-week period to obtain a serum level of 100 – 125 mg/mL. Existing lesions improved and no new lesions appeared within 8 – 10 weeks. By 16 – 20 weeks, most lesions were healed. The total duration of treatment with CSP ranged from 13 – 20 months. Patients received no systemic therapy during the 3.5 – 5-year follow-up period. There were no recurrences during this period.

While CSP is of limited benefit as monotherapy for PV, it appears more useful when used in combination with prednisone. However, better-controlled prospective studies are necessary in order to clarify its true efficacy as a steroid-sparing agent.

Mycophenolate Mofetil

Mycophenolate mofetil is an ester prodrug of mycophenolic acid, an active immunosuppressant that is a potent inhibitor of inosine monophosphate dehydrogenase. This enzyme is crucial for the *de novo* synthesis of the guanosine nucleotides necessary for DNA synthesis. B and T lymphocytes which rely on this *de novo* pathway more than on the salvage pathway, are subject to the inhibition of their proliferation and production of antibodies (31). The major side effects of mycophenolate mofetil are bone marrow suppression, diarrhea, nausea, vomiting and increased susceptibility to infection.

First approved for use in 1995 by the Food and Drug Administration, this drug is primarily used to prevent rejection in patients who have received renal and/or other organ allografts (32). Recent reports describe its use in several skin diseases, including psoriasis (33, 34) and relapsing idiopathic nodular panniculitis (35). Mycophenolate mofetil has also been used recently in the treatment of other immunobullous diseases, including bullous pemphigoid (36, 37) and pemphigus foliaceus (38).

Enk and Knop reported its use in PV, first in 1997 (39) and later, with a larger series of patients, in 1999 (40). In the latter study 12 patients with PV who had failed combination therapy with prednisolone and azathioprine received prednisolone and mycophenolate mofetil (2 g/day). Eleven of the 12 patients improved and did not relapse during the 9 – 12 month follow-up period, even after tapering of the steroid. The mycophenolate mofetil, 2 g/day, was continued during this period. One patient did not respond. Nousari and Anhalt (41) advocate dosages in the range of 2.5 – 3.0 g/day to induce remission in patients with pemphigus (both PF and PV).

The effective use of mycophenolate mofetil as monotherapy for PV was recently reported (42, 43). Bredlich et al. (42) described the cessation of new blisters in a patient with PV two weeks after the initiation of therapy with mycophenolate mofetil, 1 gram administered twice daily. Complete clearing of lesions occurred after 6 weeks of treatment. Grundmann-Kollmann et al. (43) described an additional patient who experienced complete remission after initiation of mycophenolate mofetil monotherapy. The period of remission was not specified in either of these case reports.

Use of this drug is not associated with nephrotoxicity or hepatic damage. In view of the fact that cyclosporine and methotrexate are contraindicated in certain clinical contexts, clinical trials investigating the use of mycophenolate mofetil monotherapy compared to combination therapy with prednisone and other immunosuppressive treatments appear warranted.

Chlorambucil

Chlorambucil, an alkylating agent similar to cyclophosphamide, inhibits DNA synthesis through the alkylation of nucleic acids. It preferentially affects B cells over T cells. However, bladder toxicity, observed with daily administration of cyclophosphamide, is not caused by chlorambucil. Its successful use has been reported for other diseases, including rheumatoid arthritis, systemic lupus erythematosus, juvenile rheumatoid arthritis, Wegener's granulomatosis, pyoderma gangrenosum, Behçet's disease, dermatomyositis, and bullous pemphigoid.

Its use in combination with prednisone for the treatment of pemphigus has recently been reported by Shah et al. (44). This was an uncontrolled retrospective study in which the records of 9 pemphigus patients were reviewed. Patients were started on 4 mg of chlorambucil once daily. This dosage was increased to a maximum dose of 10 mg daily, based on clinical response and toxicity. Seven of the 9 patients studied had PV. Four of these 7 patients improved and experienced remission. One patient improved while on combination therapy that also included dapsone. The two PV patients who did not improve had isolated mucosal disease without skin involvement.

It is difficult to draw conclusions from this retrospective and uncontrolled study. The authors noted a decrease in corticosteroid requirements during treatment with chlorambucil, but did not quantify the decrease for individual patients. The periods of remission were also not specified. While patients must be monitored carefully for the development of bone marrow suppression, induction of malignancy (particularly acute myeloblastic leukemia) is the most feared complication of therapy. For these reasons, a trial of chlorambucil should be reserved for those patients that have failed treatment with other immunosuppressive regimens.

Methotrexate

Smith and Bystryn (45) recently revisited the use of methotrexate as an adjuvant treatment for PV. Nine patients with PV, for whom steroid therapy could not be tapered without an exacerbation, were additionally treated with 2.5 mg of methotrexate given every 12 hours for 3 doses each week. This dose was increased by 2.5–5.0 mg every 2 weeks, if necessary. The maximum dose was 17.5 mg per week.

For 6 of the 9 patients (67%) systemic corticosteroid therapy was discontinued without a flare within 6 months of initiation of methotrexate therapy. The disease was quiescent until discontinuation of the methotrexate, at which time all 6 patients experienced a flare (mean 23 days) of disease. The authors noted that low-dose methotrexate may be a useful adjunct in PV patients for whom steroid therapy cannot be tapered without an exacerbation of disease activity. It is obvious that, at some point, adjuncts in addition to methotrexate must also be used in these patients, since no patient in the study group experienced a complete remission on this regimen.

Anti-inflammatory Drugs

Gold

In 1973 Penneys et al. (46) first reported the use of gold for the treatment of pemphigus. Aurothiomalate and aurothioglucose, the two major parenteral gold medications in the United States, are approximately 50% gold by weight (47). Auranofin, an orally absorbed compound, contains 29% gold. Parenteral gold is administered intramuscularly in a manner similar to that recommended for the treatment of rheumatoid arthritis. The initial test dose of 10 mg is followed by a 25 mg injection one week later. Subsequent weekly injections of 50 mg are administered until the patient responds clinically. Maintenance therapy consists of 50 mg injections administered at longer intervals or a lowered dose of gold continued at weekly intervals. After a cumulative dose of 1 gram has been administered, the medication is discontinued if there has been no clinical response.

Use of gold therapy is attractive for patients in their reproductive years, because carcinogenesis and infertility are not a major concern, as they are in treatment with immunosuppressive medications. However, one third of patients will experience an adverse effect during treatment (48). Fifty percent (50%) of these side effects are mucocutaneous in nature, either skin eruptions or oral ulcers. Gastrointestinal, renal and hematologic effects may be severe. Ocular, pulmonary and neurologic effects are more infrequent. Patients should be carefully monitored while on gold therapy. The results of complete blood counts with platelet counts and urinalysis should be checked prior to each injection. A complete biochemical profile should be checked before the initiation of therapy.

PV patients with mild disease may benefit from gold as monotherapy (49), but it is unclear if the use of gold induces remission in these patients or if these remissions would have occurred spontaneously. Penneys et al. (50) reported the use of gold in 18 patients with pemphigus. Three patients received gold as monotherapy, while the remaining 15 patients received combination therapy with gold and corticosteroids/immunosuppressive drugs. Seventy-two percent (72%) of the patients improved, while 44% experienced complete remission. No deaths were reported.

In 1984 Poulin et al. (51) reported the Mayo Clinic experience with gold treatment in a series of 13 patients with PV. The study involved a relatively long follow-up period, averaging 41.2 months. All patients received combination therapy with varying doses of prednisone and gold (50 mg/week). Seven patients experienced complete remission (54%) and required no further treatment. One death occurred. The average dose of gold was 2.374 g for a mean treatment period of 18.3 months. Two of these 7 patients had recurrence of the disease, 5 months and 3 months after cessation of gold therapy. The duration of the remission for the remaining 5 patients was 32 months (mean).

Gold therapy in this study was discontinued, temporarily or permanently, because of toxicity in 5 patients (38%). Proteinuria (2 patients), eosinophilia, mild leukopenia, and urticaria were reported and rapidly cleared after discontinuation of the drug.

More recently, Pandya and Dyke (52) reviewed the efficacy of gold in 26 pemphigus patients, 21 of whom had PV. In this 1998 study, 85% of the patients responded to gold therapy. A positive response was defined as an improvement in blistering, and ability to decrease prednisone dosage to less than 20 mg/day or to completely discontinue it. Only 4 patients (15%) were in complete remission at the end of the study. This is significantly lower than the complete remission rate reported in prior studies discussed above (38–54%) (34–36). Only 1 of these 4 patients had a recurrence. Seven patients discontinued prednisone and were free of disease, but they were still receiving gold. Five patients responded to gold therapy but were still receiving prednisone and gold therapy and had some degree of blistering at the end of the study. Complications from therapy developed in 42% of the patients, but these all resolved with discontinuation the gold.

Dapsone

Dapsone may be useful in the treatment of both PF and PV, although there is greater support in the literature for its efficacy in PF (53). Three of 6 pemphigus patients treated with daily doses of 100–300 mg of dapsone and prednisone improved within 2–3 weeks after initiation of dapsone therapy (11). Within 1–3 months their corticosteroid requirements were drastically reduced or eliminated. These patients included those with PV and PF, but the numbers of each were not specified.

Although the concept of using dapsone in PV to minimize the long-term adverse reactions of corticosteroids is appealing, there are only occasional reports that support its use in this disease. The addition of 100 mg of dapsone daily was followed by a full remission in a few patients that had been treated with high doses of corticosteroids in combination with methotrexate (54). One PV patient with gingival and vaginal lesions, but no skin lesions, responded well to 150 mg daily of dapsone (7). The patient also received intralesional and topical vaginal corticosteroids.

Nicotinamide and Tetracycline

The primary advantage of tetracycline and nicotinamide therapy in PV is a lower toxicity and a broader safety profile. Alpsoy et al. (55) studied 15 patients with pemphigus to determine if this combination alone was effective. Ten of the 15 patients had PV. For 2 months, 2 g of tetracycline and 1.5 g of nicotinamide were administered on a daily basis. Any concurrent therapies were discontinued. A "complete response" indicated clearing of all lesions. A "partial response" indicated clearing of 50% or more of the lesions. "No response" indicated clearing of less than 50% of the lesions. Lesions were generalized in all but one patient, who had disease localized to the oral mucosa. Of the 10 patients with PV, 2 had a complete response, 3 had a partial response, and 5 had no response. The authors concluded that this combination was not an effective alternative to the first line therapeutic options.

In a 1993 study 6 patients with PV were treated with nicotinamide, 1.5 g/day, and tetracycline, 2 g/day, with or without corticosteroids (56). Three achieved a complete response (total clearing of lesions), 2 experienced a partial response (clearing of more than 50% of lesions) and the remaining patient did not respond (clearing of less than 50% of lesions). Only 2 of the 5 patients that responded received nicotinamide and tetracycline as the only oral agents. The 3 others required a daily dose of oral prednisone ranging from 2.5–30.0 mg/day. One of these 3 patients was treated additionally with azathioprine. The follow-up period for these 6 patients ranged from 6–13 months. These results are difficult to interpret, in view of the fact that this was an uncontrolled study and because the degree of disease severity was not specified for the patients.

The efficacy of tetracycline in combination with corticosteroids, but without nicotinamide, was evaluated recently by Calebotta et al. (57). Thirteen hospitalized patients with PV receiving prednisone were administered tetracycline 2 g/day for the first month, followed by 1 g/day for the second month. Prednisone was then gradually tapered. A control group consisted of 7 patients treated with prednisone and azathioprine. In the study group, 6 patients (46%) were classified as severe, while only 2 of the 7 patients (29%) in the control group were categorized as severe.

Cessation of new blister formation occurred within 5.4 days (average) in the study group, compared to 23.7 days (average) in the control group. Reduction of prednisone could begin at 16.5 days (average) in the study group, compared to 31.2 days (average) in the control group. The authors claim that the clinical response was not associated with the location of the lesions or with the severity of the disease.

The average starting dose of prednisone was only 76.5 mg/day in the study group and 118.5 in the control group. The average remission time in the control group was more than double that of the treatment group (11.95 months versus 5.84 months). In short, it seems that the treatment group responded faster, but the control group remitted longer. This fact attenuates the significance of the lower short-term prednisone requirements in the treatment group.

Immunomodulatory Procedures

Plasmapheresis

Plasmapheresis is a procedure in which pathogenic autoantibodies are removed from the patient's blood by filtration of the plasma. Although this procedure temporarily lowers the level of circulating autoantibodies, a reactive burst of antibody production from pathogenic B cells results in a rebound effect that replaces and even overshoots the initial decrease. Therefore, to retain the decrease in circulating autoantibody levels, it is imperative to couple intensive plasmapheresis with the administration of immunosuppressive medication (6). Tan-Lim and Bystryn (58) reported 22 patients with PV who were treated with similar doses of prednisone and immunosuppressive medications, 11 of whom additionally received thrice-weekly plasmapheresis. The average level of pemphigus antibodies decreased by 83% in the patients receiving plasmapheresis, while it decreased by only 18% in the control group. More recently, 7 patients with severe PV uncontrolled by high-dose corticosteroids were treated with plasmapheresis, after which immunosuppression therapy was administered for an average of 2 months (59). High doses of corticosteroids were then administered and tapered approximately 3 months after the last plasmapheresis. Four patients achieved complete remission. Two patients experienced a partial remission, and their disease was then controllable with corticosteroids which were being tapered at the time of the report. One patient showed only short-term improvement. Although pulse intravenous cyclophosphamide was the favored immunosuppressant, pulsed corticosteroid and azathioprine resulted in remission in 2 patients.

These studies demonstrate that plasmapheresis immediately followed by immunosuppressive therapy offers a valuable treatment option for patients with PV unresponsive to conventional therapies. Plasmapheresis in combination with corticosteroids, even without additional immunosuppression, has been advocated as an effective option in pregnant patients who experience a severe exacerbation of their disease (60).

Extracorporeal Photopheresis

During extracorporeal photopheresis (ECP), a leucocyte/lymphocyte-enriched cell fraction is separated from the peripheral blood, washed in 8 methoxypsoralen and irradiated with ultraviolet A light. Treated lymphocytes are then reinfused into the patient. ECP is normally performed for 4 hours per day on 2 consecutive days every 4 weeks. The treatment is well tolerated and causes few side effects. The procedure was designed for the management of diseases mediated by malignant lymphocytes, such as cutaneous T cell lymphoma, and for other diseases mediated by aberrant lymphocyte function, e.g., autoimmune diseases. In the treatment of PV it is reserved for patients who fail to improve with conventional treatment modalities. The aim in this context is to inhibit the B-cells that produce pathogenic pemphigus antibodies.

In 1989 Rook et al. (61) treated 4 PV patients with ECP; the patients were concomitantly receiving corticosteroid and immunosuppressive therapy. All patients improved. In 1992 Liang et al. described a patient who had 70% of his skin affected by PV (62). The patient's disease resisted control with high doses of prednisone, even when used in combination with gold, cyclosporine, methotrexate, azathioprine, pulse steroids, and pulse cyclophosphamide. At the time ECP was started, the patient was receiving methotrexate (20 mg weekly), azathioprine (100 mg daily) and prednisone (240 mg daily). After seven cycles of ECP, cessation of new blister formation occurred. Prednisone was tapered and methotrexate was discontinued. Skin lesions healed.

More recently, Wollina et al. (63) reported on the use of ECP as an adjuvant in 7 patients with bullous pemphigoid or pemphigus who failed therapy with immunosuppressive medications. Three patients had PV and all three showed a complete remission of disease during 24, 34, and 10 month follow-up periods. Although these results seem promising, prospective controlled trials are necessary in order to better evaluate the efficacy of ECP.

Intravenous Immunoglobulin

Although intravenous immunoglobulin (IVIG) has been used successfully in the treatment of other autoimmune and inflammatory diseases (64), its use in the treatment of patients with PV is relatively recent. Tappeiner and Steiner (65), the first to report its use in PV in 1989, found no clinical change in 2 patients and progression of disease in a third patient, after receiving one cycle of IVIG therapy.

Subsequent studies analyzing the use of IVIG in PV reported greater success and were recently reviewed by Engineer et al. (66), who summarized the use of IVIG for PV in 8 papers which appeared since the initial report by Tappeiner and Steiner (65). IVIG was effective in 17 of the 18 patients described. It appeared to be effective if administered for 2 or more monthly cycles, each of which consisted of 5 consecutive days of treatment. For optimum results it is recommended that a minimum dosage of 400 mg/kg be administered each day of the cycle.

IVIG has a rapid onset of action and results in improvement within days of its initiation. However, the benefit appears to be short lived and disappears after only a few weeks. IVIG appears most effective when used as an adjunct to conventional therapy, and may be helpful in the treatment of patients unable to tolerate other agents. It is effective as a cortoicosteroid-sparing agent and achieved this effect in almost all the patients studied. Although its safety is not a significant issue (no side-effects from IVIG therapy were reported during the follow-up periods of the patients studied), its high cost is often a major deterrent to more widespread use. When it is available, it should be tried early in patients with severe PV that is recalcitrant to conventional therapies, or in patients at risk for developing serious side effects from prolonged corticosteroid therapy.

Preliminary Observations — Cigarette Smoking

A case of PV improved by cigarette smoking was recently reported (67). The patient had a 3-year history of PV and was not improving on combination therapy with prednisone, cyclophosphamide and dapsone. He noted that his disease flared coincident with the cessation of cigarette smoking. One week after the patient began smoking cigarettes again (15 cigarettes per day), lesions rapidly started to clear. The dapsone was discontinued. The prednisone and cyclophosphamide were tapered and discontinued over a 2-month period. The lesions were still clear 5 months after he started to smoke again.

An inverse relationship between cigarette smoking and/or nicotine and the activity level of certain diseases has been reported for ulcerative colitis, pyoderma gangrenosum, and aphthous stomatitis (68–70). Several immunomodulatory effects of smoking have been reported (71), although the exact mechanism responsible for these findings is presently unknown. Because the deleterious effects of cigarette smoking are well known and may outweigh the potential "benefits" of such a habit, research leading to more specific therapeutic interventions tailored to the exact mechanism of action may be warranted in the future.

Survey of Mount Sinai Dermatologists Regarding Therapy for Pemphigus Vulgaris

Table 2 is a summary of some treatment preferences of Mount Sinai Dermatology faculty. Of ten physicians who responded to the survey, nine indicated they treat patients with PV. All nine use prednisone or another corticosteroid as the first choice of therapy. Six of nine start therapy with prednisone and another agent such as cyclophosphamide. This survey indicates the preference among Mount Sinai dermatologists for choosing combination therapy as the initial treatment for patients with PV.

Summary and Conclusions

Inconsistencies in the responses to therapy of patients with PV may be explained in part by their heterogeneous autoantibody production in response to epidermal antigens. Patients with PV may display antibodies to the major PV antigen, the cadherin known as desmoglein 3, as expected, as well as to desmoglein 1, in a manner which is not predictable so far.

TABLE 2

A Summary of Therapy Preferences of 10 Mount Sinai Dermatologists for Patients with Pemphigus Vulgaris.

1. Do you treat patients with pemphigus vulgaris? Yes: 9, No: 1.

2. Do you use prednisone or other corticosteroid as your first choice of therapy? Yes: 9, No: 0.

3. Do you start with prednisone and an adjuvant such as cyclophosphamide? Yes: 6, No: 3.

4. What other medications have you used?
   Gold: 7
   Imuran: 5
   Methotrexate: 3
   Dapsone: 1
   Tetracycline: 1
   Nicotinamide: 1

5. How many pemphigus vulgaris patients have you treated in your career so far?
   0–15: 6
   16–30: 2
   31–45: 0
   46 or more: 1

6. How many years have you been in practice?
   0–15: 3
   16–30: 3
   31–45: 3

To date, the avidity of antibodies in PV has not been adequately studied. Avidity studies showing different binding energies of these antibodies might help explain why patients with limited disease are sometimes more difficult to bring into good control than patients with widespread disease. Research into and development of chemical molecules that can specifically turn off or down-regulate the pemphigus-specific antibody responses will no doubt offer more promise for future effective therapy in curing this potentially lethal disease.

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The Modern Age of Acne Therapy:

A Review of Current Treatment Options

Susan V. Bershad, M.D.

Abstract

This review of current acne treatments begins with the crucial discovery in 1979 of isotretinoin treatment for nodulocystic acne. This drug's approval in 1982 revolutionized therapy, since it was the first oral acne-specific drug, and it provided prolonged remissions. In addition, it may prevent the emergence of resistant bacteria, a problem linked to the traditional use of antibiotics for acne.

Patients who are not candidates for isotretinoin therapy may benefit from one of the other drugs or drug combinations reviewed, including the third-generation topical retinoids adapalene and tazarotene, retinoic acid reformulated in new vehicles, azelaic acid, and topical antibiotics. Proper selection and education of patients are essential, since serious consequences may result from poorly monitored use of antibiotics and retinoids.

Key Words: Acne, review, therapy, treatment, isotretinoin, retinoid, antibiotic, azelaic acid, adapalene, tazarotene, benzoyl peroxide.

Introduction

THE PERIOD 1945–1995 has been named the "Golden Age of Treatment" in dermatology by Thomas B. Fitzpatrick (1). These fifty years saw a great number of therapeutic discoveries, ranging from penicillin for syphilis to topical corticosteroids for psoriasis. In the field of acne treatment, the single most important event probably was the 1979 report of prolonged remissions of cystic acne attributable to 13-cis-retinoic acid (isotretinoin) (2).

In 1982, the Food and Drug Administration (FDA) approved the use of isotretinoin for treating recalcitrant nodulocystic acne. Unlike traditional antibiotic treatment, isotretinoin's sole approved indication is cystic acne. Its effect lasts months to years after a 20-week course, a claim that no other acne medication can match. Also, its use does not promote antibiotic-resistant bacteria, an important concern (3).

Since isotretinoin is reserved specifically for severe acne, it has not made other acne treatments obsolete. Yet it appears to provide an acne treatment that is comfortable, safe, effective, and lasting.

Acne: Definition, Demographics and Pathogenesis

Acne is a chronic inflammatory condition of the pilosebaceous unit. The comedo, a plug of sebum and keratin lodged in the follicular duct, is its primary lesion. Comedones appear clinically as blackheads and whiteheads. When a closed comedo or microcomedo causes the follicular wall to rupture, an inflammatory reaction ensues, resulting in clinically evident papules, pustules, nodules and cysts. The term "cyst" is a misnomer that refers to a pus-filled acne lesion greater than 5 mm in diameter, in which the wall is composed of inflammatory cells and scar tissue.

The typical clinical picture of acne is an eruption located on the face, with the upper trunk often being affected as well. Adolescents and young adults are most often afflicted, with estimates of 85–100% of those aged 12–24 being affected, at least intermittently, during those years (4, 5). Within the adolescent group, the frequency and severity of acne, as well as its tendency toward scarring, is greater in males than in females. However, the persistence of acne into adulthood is more common in females (6).

Contrary to popular belief, hygiene plays at most a minor role in the etiology of acne, and diet appears to have little or no influence. However, true acne can be exacerbated by external factors such as friction ("acne mechan-

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ica") (7) and pore-clogging cosmetics ("acne cosmetica") (8). The etiology of acne lies in a confluence of several factors which together produce clinical acne. Research suggests that genetic control, along with the stimulation of androgenic hormones, is responsible for abnormal sebum secretion (9, 10). The latter, together with faulty corneocyte occlusion of the pilosebaceous orifice, produces comedonal acne (11). The anaerobic diphtheroid *Propionibacterium acnes* is believed to play a pivotal role in converting comedonal acne to inflammatory acne. Previously *P. acnes* was thought to incite inflammation by breaking down neutral sebaceous lipids into free fatty acids, but newer research favors a direct role for *P. acnes* in neutrophil attraction (12).

Treatment of Acne

Today's therapeutic modalities for acne are aimed at one or more of its pathogenic precipitants, which include androgenic hormonal stimulation, hypersecretion of sebum, faulty occlusion of the follicular orifice, *P. acnes* colonization, and inflammation. Combination therapy, therefore, is the usual approach, with isotretinoin treatment being the notable exception.

Comedonal Acne

When open and closed comedones are the principal manifestations of acne, there is no substitute for the immediate results achieved with acne surgery, which is the manual extraction of impacted comedones, performed in the physician's office. Most patients benefit by having this procedure performed at 3–6 week intervals until topical medications take effect. Patients should be discouraged from attempting this at home, due to the risk of infection and the potential for scarring due to excessive trauma to the skin.

The most effective topical medications for comedonal acne are the so-called keratolytic agents, which target faulty occlusion of the follicular orifice. This group includes the retinoids, azelaic acid, and the alpha-hydroxy acids (AHAs).

Retinoids

Topical Vitamin A acid (tretinoin, all-trans-retinoic acid) and its synthetic analogs, termed retinoids, comprise the most potent group of currently available keratolytic agents. Medications in this group include topical tretinoin, adapalene and tazarotene, as well as oral isotretinoin. Considerable current research is focused on this category.

Tretinoin preceded the others in this class by a decade or more, becoming available as a topical acne treatment in the United States in 1971. Tretinoin exerts its effects by increasing the turnover of follicular epithelial cells, thus normalizing keratinization (13). This leads to the extrusion of comedones and also accelerates corneocyte shedding, thereby inhibiting comedo formation (14).

Early formulations of tretinoin tended to cause excessive skin irritation, due to the high concentration of the active ingredient in a penetrating hydroalcoholic vehicle. Now available are a number of formulations which utilize a lower tretinoin concentration (0.025%) and cream vehicles which are designed to be more emollient and less penetrating. Two of the newest topical tretinoin products are based on slow-release delivery systems (15). One of these contains tretinoin (0.025%) in a gel or cream base containing polyolprepolymer-2, a large-polymer compound that delays absorption of the active ingredient into epidermal cells. The second formulation designed to slow delivery is a tretinoin (0.1%) gel, in which the active ingredient is incorporated into microsponges, which are macroporous beads 10–25 microns in diameter.

Despite these improvements, the use of tretinoin in dermatology practice is often limited by local skin irritation. In addition, the onset of improvement is relatively delayed and variable — one to three months is common (16). Some patients experience clinical worsening after 2–4 weeks of treatment (17), when the extrusion of comedones can elicit a pustular reaction. Tretinoin also increases sun sensitivity, necessitating regular sunblock use.

Two recently developed topical polyaromatic retinoids, adapalene and tazarotene, may provide therapeutic advantages over tretinoin. These new agents have molecular configurations that are selective for nuclear retinoic acid receptors. It is theorized that these receptors, when activated, affect keratinocyte differentiation and block inflammation (17–19).

Adapalene is a synthetic naphthoic acid derivative. Its mechanism of action is twofold: first, it inhibits comedo formation through its ability to bind to retinoic acid receptors and modulate cell differentiation; and second, it possesses direct anti-inflammatory activity

(20). Adapalene is available in gel, solution and cream formulations containing 0.1% active agent.

In a multicenter study of more than 300 patients, adapalene (0.1% gel) was compared to tretinoin (0.025% gel) for efficacy and side effects. Adapalene produced significantly greater lesion reduction than tretinoin and caused less local skin irritation (21).

Adapalene shares with other retinoids the adverse effect, in certain patients, of an inflammatory acne flare toward the end of the first month of therapy. This risk can be reduced by introducing adapalene or tretinoin gradually. The retinoid is generally applied 2–3 times per week initially, and increasing to nightly use over a period of about 2 months. Oral or topical antibiotics are often combined with retinoid therapy, due to their ability to inhibit the inflammatory process.

Tazarotene, a synthetic acetylenic retinoid, was introduced in 1997 as a gel to treat psoriasis. After topical application, it is rapidly converted to its active metabolite, tazarotenic acid. Two large clinical studies found tazarotene 0.1% gel to be more effective than vehicle in the treatment of acne (22), but erythema and irritation were common side effects. A tazarotene cream is now available as well. A new method of acne treatment, called short-contact tazarotene therapy, has been developed by the author. This method involves applications once or twice daily of tazarotene (0.1%) gel for 2–5 minutes per application, followed by thorough rinsing with warm water. In a pilot study of this method, 20 patients with facial acne applied open-label tazarotene 0.1% gel using the short-contact method. Fourteen patients (70%) achieved at least 50% reduction in acne lesions within 12 weeks of therapy (see Figure) (23). There was no control group in this early study, but subsequent vehicle-controlled clinical trials support the efficacy of this novel method (22).

Azelaic Acid

Azelaic acid is a naturally occurring dicarboxylic acid. Available in a 20% cream formulation, it has been demonstrated to prevent follicular hyperkeratosis, thereby inhibiting comedogenesis (14). It also has antimicrobial activity, being bacteriostatic against *P. acnes* and *Staphylococcus epidermidis* (24). Furthermore, it does not appear to induce resistant *P. acnes* (25).

Clinically, azelaic acid 20% cream has been shown to have efficacy comparable to other topical medications (25). It is associated with a low rate of adverse effects, the most common being local itching and burning sensations.

Alpha-Hydroxy Acids

AHAs are carboxylic acids that contain a hydroxy group on their second (alpha) carbon. These occur naturally in sugar cane, fruits, and milk products. The most useful AHAs in dermatological practice are glycolic acid, lactic acid, and gluconic acid (gluconolactone).

Since the 1970s, it has been known that AHAs facilitate desquamation of the stratum corneum (26). This finding has led to the clinical use of AHAs in the treatment of comedonal acne. Because these compounds are not patent-protected drugs under strict FDA control, large well-controlled trials are lacking. However, there is evidence suggesting acne improvement with AHAs, especially glycolic acid and gluconolactone (27, 28).

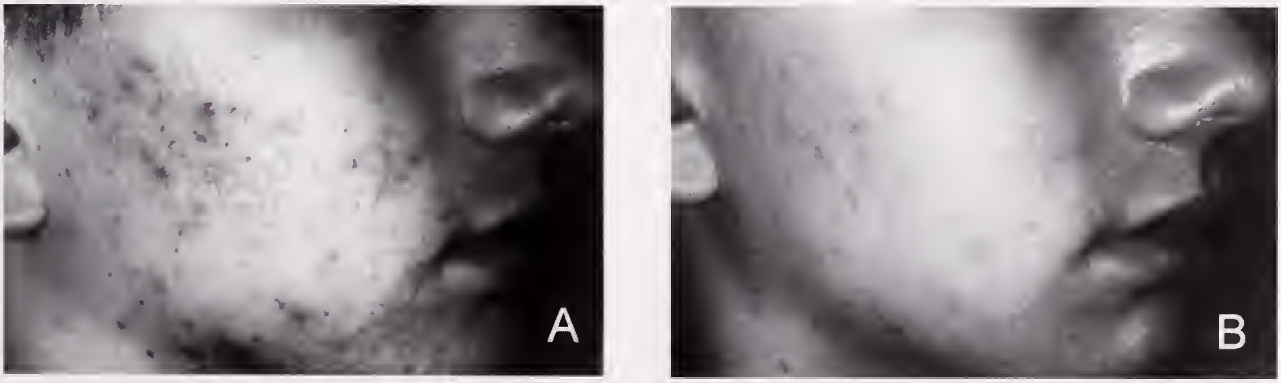

Figure. **(A)** A 17-year-old patient, previously untreated for acne. **(B)** After 7 weeks of short- contact tazarotene therapy (23).

AHAs currently available for acne treatment consist mainly of 5 – 10% glycolic acid in water-based lotions or hydroalcoholic solutions. Peeling agents containing 30 – 50% glycolic acid may be used in the office setting (28).

Lower concentrations of AHAs derive their therapeutic usefulness in part due to the lower likelihood of causing skin irritation. As non-prescription products, they have found their way into the treatment of mild acne, particularly in pre-adolescents and adult females.

Inflammatory Acne

Since the primary lesion of all forms of acne is the comedo, a majority of acne patients can benefit by using keratolytic agents. In addition, when the predominant lesion type is the inflammatory papule or pustule, the traditional mainstays of treatment are topical and systemic antibiotics.

"Combination therapy" for acne is generally defined as ongoing treatment with two or more agents applied at different times. Commonly, a topical antibiotic is applied in the morning and a keratolytic agent is applied at bedtime. Because antibiotic-resistant *P. acnes* and staphylococci are well documented (29, 30), a better regimen might be twice-daily antibiotic followed by a keratolytic agent at bedtime. If two agents are applied at the same time, care must be taken to ensure that the two are compatible and that they are not thereby diluted to ineffective strengths. For example, tretinoin is inactivated by benzoyl peroxide, while adapalene and tazarotene are not.

Benzoyl Peroxide

Benzoyl peroxide is a potent bactericidal agent that is widely available in prescription and non-prescription acne products, including gels, lotions and cleansers. In concentrations of 2.5 – 10%, it effectively reduces *P. acnes* and free fatty acids in sebum (31). There is evidence that it reduces comedones (14, 32), in addition to improving inflammatory acne (33).

Common adverse effects include dry skin and bleaching of the skin and fabrics. Occasionally, true contact allergy occurs. Recent concerns that benzoyl peroxide enhances carcinogenesis in laboratory animals (34) are thought to be of little relevance to humans by the scientific community (35).

Topical Antibiotics

The topical antibiotics clindamycin and erythromycin have been available as hydroalcoholic solutions for about two decades. Newer formulations intended to reduce skin irritation include hydrophilic gels and lotions. The 1990s have seen an increase in the popularity of the pledget application system, which is often more convenient than the traditional applicator bottle.

These agents have been shown to reduce colonization of *P. acnes*, and they may also possess direct anti-inflammatory effects via suppression of neutrophil chemotaxis (36, 37).

A clinical study showed that two different topical solutions, one containing 1.5% erythromycin and the other containing 1% clindamycin, were therapeutically equivalent for acne (37). Further, in a double-blind clinical trial, therapy with clindamycin 1% solution was found to be as effective as oral tetracycline 250 mg twice daily (38).

Two fixed combination gels, the first containing erythromycin 3% with benzoyl peroxide 5% and the second containing clindamycin 1% with benzoyl peroxide 5%, have been found to be superior to their individual components for acne treatment (32, 39, 40). An added advantage of these combinations may be a reduction in drug-resistant *P. acnes* (29). Erythromycin is also available as a 2% solution with zinc, a suppressor of inflammation. A recent study suggests that zinc may act mainly as an inhibitor to penetration, leaving the antibiotic on the skin surface longer (41). The clinical correlate of this finding is unclear.

Other topical antibiotics that are useful in acne treatment include metronidazole, elemental sulfur and sulfur compounds. These may act mainly as direct inhibitors of inflammation; they are generally considered to be more useful in treating acne rosacea, a condition with early inflammation, than true acne, which starts with comedogenesis.

Systemic Antibiotics

There has been little change in systemic antibiotic therapy for acne in recent years. Oral drugs are indicated for moderate-to-severe forms of acne, particularly those with a potential for scarring.

Effective systemic therapies for acne include: tetracycline and its relatives minocycline and doxycycline; erythromycin; azithromycin;

and trimethoprim alone or in combination with sulfamethoxazole (42). Traditionally, systemic antibiotic treatment has been initiated in the modest-to-low-dose range, which is then tapered over a period of weeks to months. It may be time to reconsider this strategy, in recognition of the increase in antibiotic-resistant bacteria, which occurs not only in acne patients, but also in their household contacts (29). A suggested alternative is full-dose antibiotic treatment for 2–3 weeks, given at several-month intervals, for acne flares.

Each oral medication has known side effects, the most notable in this category being: phototoxicity from the tetracycline group, especially doxycycline; vertigo-like dizziness from minocycline; gastrointestinal distress from erythromycin; and drug eruptions, including Stephens-Johnson syndrome, from trimethoprim-sulfamethoxazole. In addition, all oral antibiotics predispose to *Candida* infections, particularly vaginitis.

A recent study of the safety of the tetracycline-related antibiotics showed minocycline to have a greater tendency than tetracycline and doxycycline to cause rare adverse effects, including hypersensitivity reactions, serum-sickness-like reactions, drug-induced lupus, and single organ failure (43). While minocycline is generally considered safe for long-term use (44), these rare but serious reactions, as well as its higher cost, must be taken into account.

Hormonal Therapy

Numerous studies have shown a direct correlation between serum androgen levels and acne (45, 46). Androgens increase sebaceous gland activity and may also cause hyperkeratosis of the pilosebaceous gland (47). It has also been hypothesized that sebaceous glands of acne-prone individuals are hyperresponsive to normal serum androgen levels (48).

While oral contraceptives have been used successfully in acne treatment for decades, this mode of therapy for female patients made a recent breakthrough. For the first time, in 1997, the FDA approved a triphasic, combination oral contraceptive (OC), which contains norgestimate 0.215 mg and ethinyl estradiol 0.035 mg, to be used specifically for acne treatment. This decision followed a large, multicenter study which showed that this OC reduced acne lesion counts by more than 50% in female subjects, compared with lesion reductions of about 26% in controls (49). The progestin in this combination has low intrinsic androgenicity and minimal antiestrogenic effects (50).

It should be noted that acne improvement during treatment with norgestimate/ethinyl estradiol might take 3–4 months to become apparent (49). The principal adverse effect noted in this study was nausea. As expected, OC treatment was protective against pregnancy and appeared to alleviate dysmenorrhea, which was more common in the control group. The chief limitation of anti-androgen therapy for acne is the obvious one: it cannot be used with male patients.

An alternative drug for treating hormonal acne in women is spironolactone (51), which can be combined with OC therapy. Other anti-androgenic therapies that may prove useful in the future include cyproterone acetate, flutamide, finasteride, and gonadotropin-releasing hormone agonists (52, 53).

Nodulocystic Acne

All of the treatments mentioned previously can be used with some success in severe, nodulocystic acne. Particularly useful are oral antibiotics combined with topical keratolytic agents, as well as hormonal therapy in women. While oral and intralesional corticosteroids are useful as temporary measures to help control severe outbreaks (54), chronic corticosteroid use is contraindicated in acne.

Isotretinoin

After two decades of retinoid research, isotretinoin (13-cis-retinoic acid) remains the treatment of choice for recalcitrant nodulocystic acne and the more severe variant, acne conglobata (55). Isotretinoin causes de-differentiation of the sebaceous gland, suppressing sebum production to pre-adolescent levels (56). As with other retinoids, it also promotes shedding of keratinocytes. In addition, colonization with *P. acnes* subsides, due to disappearance of sebum.

Isotretinoin's clinical effect on acne is dramatic, often reducing lesion counts by 90% or more within three months. Its results are prolonged, with one 20-week course producing significant improvement for 3 years or longer in about 80% of patients (57).

The usual dosage range of isotretinoin is 0.5–2.0 mg/kg/day. Studies have shown doses as low as 0.1 mg/kg/day to be effective, but acne relapse rates are high, approaching 50%, at this dose (58). As a predictor of the final outcome, researchers have observed that the 20-

week cumulative dose is more important than the daily dose. In 1997, a consensus regarding isotretinoin dosage was reached among international acne experts (59). Their guidelines recommend a cumulative dose of 120 mg per kilogram of body weight over a single 20-week course of therapy, using the original oral formulation of isotretinoin. Currently, an ultramicronized form of oral isotretinoin is being introduced for the purpose of more efficient absorption of the active ingredient. It is unclear how this new product may impact dosing guidelines.

Because isotretinoin has a half-life of 10–20 hours, 24-hour dosing intervals are adequate, but twice-daily dosing may reduce side effects.

Although 15–20 weeks is the standard course of isotretinoin, practitioners who follow cumulative dosing guidelines may choose to vary the length of treatment slightly. FDA guidelines, however, still include an 8-week drug-free period following 20 weeks of isotretinoin.

Neither federal guidelines nor common sense supports the concept of "pulse-dosing" with isotretinoin. It is likely that the risk of teratogenicity, isotretinoin's most serious side effect (60), would increase when drug treatment is prolonged, interrupted or inadequately monitored. In a recent study of intermittent dosing with isotretinoin for one week each month over 6 months, resolution of acne was impressive, about 90%, but the 12-month relapse rate was close to 40% (61).

Adverse effects from isotretinoin are seen in virtually 100% of its users but generally subside one to three weeks after cessation of therapy. Dryness of the skin and mucous membranes, and chapped lips (retinoid cheilitis) are universal at therapeutic doses. Patches of eczema (retinoid dermatitis) occur commonly, typically on the dorsal hand and forearm. These complaints are managed with moisturizers, greasy topical corticosteroids, and dosage adjustment, if necessary. Skin fragility and susceptibility to sunburn are frequently reported. Dry eyes, nosebleeds, hair shedding, myalgias and arthralgias are not uncommon.

Recently, several cases of psychological depression and even suicide have been reported among patients taking isotretinoin (62). Paradoxically, previous studies had shown an improvement in well-being and self-esteem (63). Whether isotretinoin plays a causal role with regard to these symptoms is unclear, as a recent large, population-based study failed to show an increased risk of depression in isotretinoin users compared with other acne patients (64).

Patients on isotretinoin may experience a temporary flare-up of acne after 2–4 weeks of therapy. As is the case with topical retinoids, gradual introduction of the drug, along with patience, usually leads to a favorable outcome. A rare but troubling event that may occur during isotretinoin therapy is the onset of acne fulminans (65). This condition is a painful, severe exacerbation of cystic acne with exuberant granulation tissue and scarring. Acne fulminans can be managed with variable success by temporarily decreasing the isotretinoin dose and treating concurrently with a short course of systemic corticosteroid (66). Dapsone may also be effective (65).

Tetracycline derivatives and vitamin preparations containing vitamin A should be avoided during isotretinoin therapy, since these medications may increase the risk of pseudotumor cerebri (44), a rare side effect of isotretinoin.

The most notable systemic problems with isotretinoin are its teratogenicity and its effect on serum lipids. The former cannot be overemphasized: the risk of birth defects mandates careful patient selection, contraceptive counseling, and strict monitoring of women who may become pregnant. Isotretinoin is not mutagenic, and federal guidelines suggest that pregnancy is safe one month after drug cessation. Patients may not donate blood during isotretinoin therapy due to its teratogenic potential. Two negative pregnancy tests are now required prior to initiation of isotretinoin therapy, and monthly testing is mandatory for sexually active females during treatment.

Serum lipid and lipoprotein alterations are common, with elevation of triglycerides being reported most frequently (67). Mean triglyceride levels have been shown to increase by about 50% within 2–3 months on the drug, and cholesterol by about 15%. Overweight patients have an increased risk of isotretinoin-induced hypertriglyceridemia. Blood work, including fasting triglyceride and cholesterol levels, should be performed at baseline and at 2–4 week intervals during isotretinoin therapy (56).

Isotretinoin has been linked with premature closure of the epiphyses of long bones in laboratory animals (63). For this reason, some physicians prefer to reserve its use for patients past their growth spurt. A baseline serum alkaline phosphatase level is often helpful to assess the level of adolescent bone growth.

Some degree of acne relapse after isotretinoin treatment occurs in a significant number of cases, perhaps as many as 60%

within three years (57). Patients at particular risk for recurrence are adolescents under the age of 18, women with hormonal acne (68), and patients whose cumulative dose is less than 100 mg per kilogram (57). Relapses are usually minor and can be managed with conservative topical therapy. About 20% of patients have acne relapses severe enough to warrant retreatment with isotretinoin after a drug-free interval of at least eight weeks.

Discussion and Summary

With so many acne treatments available, there are four principal reasons why this disorder remains a common affliction. First, not everyone pursues medical treatment for acne. Second, the health practitioner might not select the optimum therapy for a given patient. Third, the patient may not understand or comply with the treatment regimen. And finally, the perfect drug for acne — one that is safe and efficacious for all varieties of the disorder — does not exist.

Physicians carry the responsibility of educating the public, as well as health insurance carriers, on the need for acne treatment. Acne is a physically and emotionally debilitating disorder that requires medical care, regardless of cost-cutting trends in our health-care system.

While the physician must choose wisely from the array of treatment options, dermatology care remains as much an art as a science. Effective physician-patient communication is crucial if any regimen is to provide its maximum benefit. Patients must be educated to apply topical therapies to nonlesional skin as well as to blemishes, and to understand that all acne medications are essentially prophylactic. They should also be taught the importance of continuing treatment when the condition is at its best. Using topical and oral antibiotics in an "ad lib" fashion may lead to resistant bacteria and chronic treatment failure.

Finally, certain conclusions can be made about current medications, imperfect as they may be. Topical therapy should be relied upon when possible, to minimize side effects. Combination therapy with a keratolytic agent and a topical antibiotic is a rational approach. While oral antibiotics have an important role, care must be taken to avoid their haphazard use.

Isotretinoin has revolutionized acne therapy. Its use requires expert patient selection, education, and monitoring. Until the next generation of therapeutic options is realized, isotretinoin remains the choice for difficult cystic acne.

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Pyoderma Gangrenosum

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Abstract

Pyoderma gangrenosum (PG) is an idiopathic, painful and destructive condition that usually presents as an ulceration on the pretibial region of the legs. It primarily affects patients with inflammatory bowel disease, arthritis, myeloproliferative disorders and chronic hepatitis, and occasionally affects patients with other conditions, but it may also occur without any associated illness. Since there are no specific serologic or histologic markers for PG, it must be diagnosed clinically. Treatment usually involves immunosuppressant therapy as well as treatment of the underlying disease. The course of PG is unpredictable, and prognosis depends on the extent of the skin lesions at the time of diagnosis, underscoring the need for early and aggressive management.

Key Words: Pyoderma gangrenosum, inflammatory bowel disease, neutrophilic dermatoses, chemokines, cyclosporine, tacrolimus, corticosteroids.

Pyoderma gangrenosum (PG) is an uncommon inflammatory skin disease that typically presents as a painful, destructive ulceration on the anterior surface of the legs. It was originally described by Brocq in 1916 (quoted in Bennett) (1) and later by Brunsting et al. in 1930 (2). A number of contributions to the study of PG have come from the Mount Sinai School of Medicine. Greenstein et al. studied the extra-intestinal manifestations of inflammatory bowel disease (IBD) in a large series of patients and provided data on the prevalence of PG in this group of disorders (3). Regional enteritis or Crohn's disease, a disease frequently associated with PG, was first described at Mount Sinai (4), and the occurrence of PG in this condition was reviewed by Libin et al., also from this institution (5). Talansky et al. studied the effect of intestinal resection on the course of PG (6) and Keltz et al. reviewed peristomal pyoderma gangrenosum (7). Freedman et al. described PG associated with anticardiolipin antibodies in a pregnant patient (8) and Klein et al. described three patients with diverticulitis, arthritis and PG (9). Hecker and Lebwohl (10) reported the efficacy of thalidomide in the treatment of recalcitrant PG.

The characteristic PG ulcer expands centrifugally and has a necrotic center filled with blood, pus and granulation tissue (Fig. 1). The necrosis may be superficial or deep, involving skin, subcutaneous tissue, fascia, and rarely muscle. The boggy, raised border is characteristically deep red, purple or dusky blue with an undermined, ragged, overhanging edge (2). The advancing border is surrounded by an erythematous halo and may sometimes be studded with pustules (Fig. 2). On palpation, a purulent exudate can be expressed from sinus tracts at the base of the lesion and from under the violaceous border. About 40% of the cases of PG follow minor trauma, a phenomenon referred to as pathergy (11–13). In Brunsting's original paper, the condition was described as usually beginning with single or multiple pustules that ulcerated — but the primary lesion can also be a papule, erythema nodosum-like nodule or plaque (Fig. 3). The ulcer frequently expands

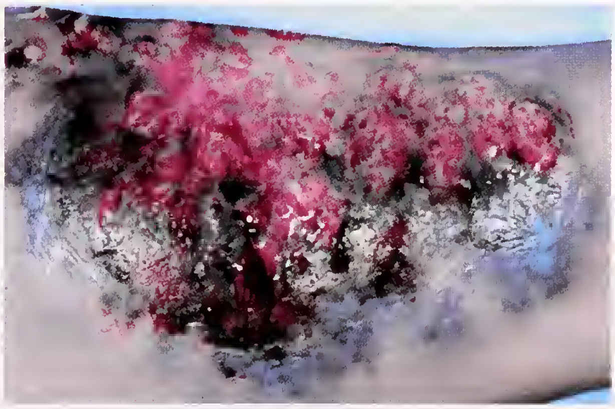

Fig. 1. Large ulceration involving pretibial area of leg. Note central blood and pus with region of deep necrosis.

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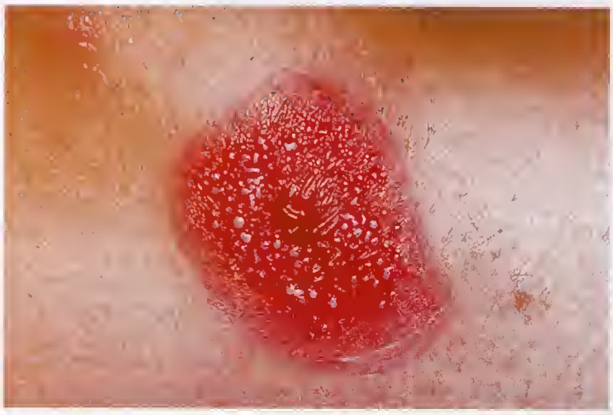

Fig. 2. Pyoderma gangrenosum: Advancing erythematous border with pustulation.

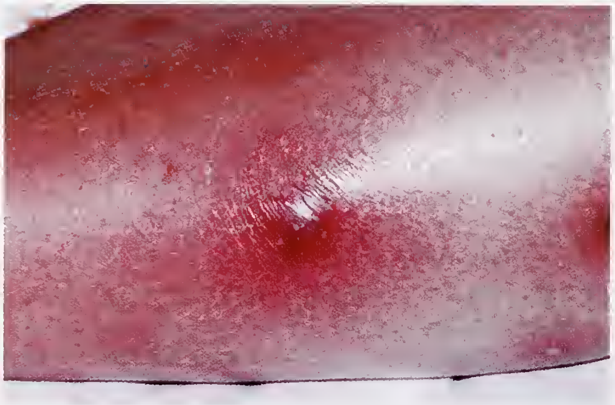

Fig. 3. Pyoderma gangrenosum: Early lesion beginning as erythematous plaque with a few pustules.

rapidly, resulting in massive tissue destruction, or it may extend slowly over weeks to months.

Lesions of PG are usually situated on the anterior aspect of the legs, but lesions can occur anywhere on the body, including the head and neck, abdomen and genitals (14, 15). There may be involvement in a peristomal distribution (Fig. 4) in patients with Crohn's disease or ulcerative colitis who have undergone ileostomy (7). This is possibly the result of a pathergic response to stomal appliances or fecal irritation. In addition to being uncomfortable, PG interferes with appliance adhesion. Involvement of the vulva, penis or perineal area can result in severe mutilation.

Ulcerations may be single or multiple. Adjacent PG lesions often become confluent, to form a single large ulcer with a polycyclic, scalloped border. The resulting lesion varies in size from a few centimeters to almost total limb involvement. Typically, severe pain and tenderness are associated with PG. Before complete healing has occurred, pus may be expressed from openings in the re-epithelialized skin. PG ultimately heals with an atrophic, cribriform scar.

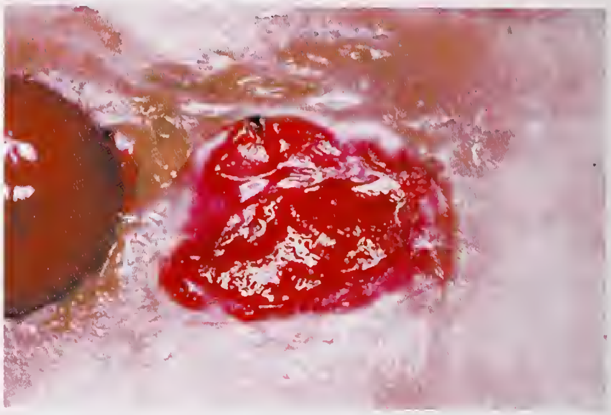

Fig. 4. Peristomial pyoderma gangrenosum in a patient with ulcerative colitis. There is early re- epithelialization at the borders following perilesional corticosteroid injection.

Etiology

The etiology of PG is currently unknown. Brunsting, who considered PG to be an infectious process, referred to it as a pyoderma or ecthyma (1). Although cultures of early lesions are usually sterile, ulcers of longer duration may yield positive cultures for staphylococci and streptococci as a result of colonization and wound superinfection. Although removal of these colonies may aid wound healing, they are thought not to be involved in pathogenesis (16). Bacteria may, however, promote further tissue destruction, cellulitis and sepsis. The clinical spectrum of PG has been expanded to include atypical lesions, and there have been cases that occurred simultaneously with acute febrile neutrophilic dermatosis (Sweet's syndrome). Whether typical and atypical PG are precisely the same disease process remains to be determined.

The association of PG with immunologic disorders such as inflammatory bowel disease, paraproteinemia and rheumatoid arthritis, and its clinical response to immunomodulating agents such as corticosteroids and cyclosporine suggest an immune etiology. While several immunological abnormalities have been described in patients with PG (17–19), these findings must be interpreted cautiously, owing to the small number of cases studied. How a variety of diverse conditions with distinct immune abnormalities can lead to the final common pathway of neutrophilic infiltration and tissue destruction is not understood.

Immune defects that have been described include cell-mediated, humoral and complement abnormalities, immune complex deposition, and the possible existence of circulating factors influencing lymphocyte function. It is important to note that no immune defect common to all, or to a majority of cases, has been delineated. While altered, delayed-type hypersensitivity has been noted in several patients, many patients have had normal function (20). In one case, altered type III hypersensitivity was associated with a circulating serum factor that inhibited *in vitro* immunologic responses of the patient's lymphocytes and those of normal controls (20).

An association of PG with benign monoclonal gammopathy, especially of the immunoglobulin A (IgA) type, has been described in some patients. Abnormalities of neutrophil and monocyte chemotaxis and phagocytosis have also been described (21). Mast cell activation has been implicated in the etiology of PG in one report (17). Interestingly, decreased neutrophil chemotaxis has been associated with elevated IgA levels in psoriasis, PG and Sweet's syndrome (22). This is thought possibly to be of significance in other dermatoses with neutrophilic infiltration, such as dermatitis herpetiformis, IgA pemphigus and Henoch Schonlein purpura. Moreover, neutrophils may undergo chemoattractant-induced upregulation of IgA receptors and concomitant IgA-induced increases in superoxide production *in vitro* (23).

The presence of pus as a clinical hallmark of PG and the large neutrophilic infiltrate on biopsy suggest that tissue destruction is mediated by the polymorphonuclear leukocyte. In disease states characterized by neutrophilic destruction of tissue, an oxidizing environment is created by neutrophil oxidants, such as hypochlorous acid (HOCl), which facilitates unregulated expression of neutrophil proteases such as elastase, collagenase or gelatinase (24).

At the same time, biopsy of the advancing edge of PG lesions demonstrates a lymphohistiocytic infiltrate, and more recently these lesions have been noted to contain activated mast cells (17). Snyder (25) has suggested that the mononuclear infiltrate on the advancing margin may initiate the chemotaxis of neutrophils. There have been conflicting reports regarding the deposition of immune reactants in PG. Dantzig (26) found no deposition of IgG, IgA, IgM, IgE or C3 in two patients with PG, whereas Su et al. (27) found deposition of C3 and IgM in the papillary and reticular dermis and proposed a lymphocytic vasculitis. Immune deposits have been reported by others (28, 29). Although these immune deposits may play a role in the development of PG, it is possible that they are an epiphenomenon of the inflammatory process.

Recent work suggests that when inflammation occurs in the skin, inflammatory cell infiltration follows the upregulation of adhesion molecules on endothelial cells of post-capillary venules (30). In certain neutrophilic processes, endothelial cell activation by interleukin-1 (IL-1) produced by resident macrophages and tumor necrosis factor alpha (TNFα) produced by macrophages and lymphocytes acting on some stimulus, lead to the expression of E-selectin and intercellular adhesion molecule-1 (ICAM-1) on the endothelial cell surface. This promotes adhesion and subsequent rolling of neutrophils on the endothelial surface. Chemotactic cytokines (chemokines) such as IL-8, ENA78, GROα, GROβ and GROγ are generated by macrophages, fibroblasts, endothelial cells and epithelial cells in response to TNFα or IL-1 in areas of inflammation (31). These chemokines cause directed extravasation of neutrophils. Mast cells, as have been identified in PG, may play a role in the expression of P-selectin (CD62P) on endothelial cell surfaces (15). Extravasated neutrophils can induce additional neutrophil recruitment as a result of their ability to produce IL-8, platelet activating factor (PAF) and leukotriene B_4 (LTB_4). This scenario has not as yet been demonstrated in PG, but a positive feedback loop for neutrophilic infiltration has been suggested in psoriasis, another dermatosis in which neutrophils are prominent (32).

The rapid improvement of PG with cyclosporine therapy suggests the involvement of T-lymphocytes in the pathogenesis of PG. The predominant mechanism of action of cyclosporine is inhibition of T-lymphocyte activation, with profound reduction of IL-2 production. The target of immunosuppressive drugs such as cyclosporine and tacrolimus is held to be nuclear factor of activated T cells (NF-AT). This cyclosporine-sensitive transcription factor is expressed in T cells, B cells, natural killer (NK) cells, mast cells, monocytes and macrophages, but is not found in neutrophils (33). On the other hand, since cyclosporine may also inhibit monocyte and neutrophil phagocytosis and neutrophil superoxide production, its effects are not entirely limited to lymphocytes (34, 35). One research group has called the neutrophil an "obeying cell" driven by other cells of the immune system (36).

Although there have been no systematic studies of the pathergy reaction in PG, such studies have been performed on another neutrophilic dermatosis, Behçet's disease. One such study (37) reported subcorneal pustule formation and a variable, dense mononuclear infiltrate of T-lymphocytes and monocytes around vessels and skin appendages extending into the deep dermis. Endothelial cells expressed E-selectin and ICAM-1, but not vascular cell adhesion molecule-1 (VCAM-1). The authors suggested that the pathergy reaction might result from an antigen-independent, delayed-type, hypersensitivity-like reaction. This would differ from the normal response to trauma by a disproportionate release of inflammatory cytokines from injured keratinocytes, that might later be amplified by infiltrating activated lymphocytes.

Another possibility is that an unidentified autoantigen might be present in the skin of patients with PG. Das et al. (38) identified an epithelial autoantigen in ulcerative colitis that was present in colon, skin and biliary epithelium and suggested this might be a link in the pathogenesis of ulcerative colitis, pyoderma gangrenosum and sclerosing cholangitis.

PG commonly occurs in patients with other disorders such as inflammatory bowel disease, arthritis (39), chronic hepatitis (40, 41) or myeloproliferative disease (1, 2, 16, 42–44) (Table 1). Although it has been reported with a multitude of other conditions, including two cases with HIV infection, some of these associations are undoubtedly coincidental. IBD is the most commonly reported co-morbid condition; it has been noted in 30–60% of cases. Although 50% of PG cases were linked with ulcerative colitis in early reports, more recent series have suggested that this association is less common (1, 17, 45–47). Greenstein et al. (3), at this institution, found that five percent of patients with ulcerative colitis developed PG. In various studies, from 0.15% to 1.5% of patients with Crohn's disease have developed PG (46, 48, 49). In Greenstein's series, 1.4% of patients with Crohn's disease developed PG. Up to 50% of cases are idiopathic.

Visceral involvement by PG has been reported rarely, including pulmonary, bone, liver and spleen involvement (50). Kasuga et al. (51) described a patient with multiple aseptic pulmonary nodules that on biopsy showed chronic, nonspecific, inflammatory changes with neutrophils and lymphocytes.

TABLE 1

Diseases Associated with Pyoderma Gangrenosum

Common Associations
- Inflammatory bowel disease
    - Chronic ulcerative colitis
    - Regional enteritis, granulomatous colitis (Crohn's disease)
- Arthritis
    - Seronegative with inflammatory bowel disease
    - Seronegative without inflammatory bowel disease
    - Rheumatoid arthritis
    - Spondylitis
    - Osteoarthritis
- Hematologic diseases
    - Myelocytic leukemias
    - Hairy cell leukemia
    - Myelofibrosis, agnogenic myeloid metaplasia
    - Monoclonal gammopathy (IgA)

Rarely Reported Associations
- Chronic active hepatitis
- Myeloma
- Polycythemia rubra vera
- Paroxysmal nocturnal hemoglobinuria
- Takayasu's arteritis
- Primary biliary cirrhosis
- Systemic lupus erythematosus
- Wegener's granulomatosis
- Hidradenitis suppurativa
- Acne conglobata
- Malignancy
- Thyroid disease
- Pulmonary disease
- Sarcoidosis
- Diabetes mellitus

Reprinted with permission from: Callen JP. Pyoderma gangrenosum and its related disorders. Adv Dermatol 1989; 4:51–65 (16).

PG is a relatively rare condition. It can affect any age group, but is most common in the third, fourth and fifth decades of life. Children are affected less commonly, but have disease associations similar to those of adults, including IBD, arthritis and leukemia. Some cases in children have been reported in association with hypogammaglobulinemia (52). Rarely, PG in children may be complicated by chronic, recurrent, multifocal osteomyelitis (53). According to some authors, females and males are equally affected, but other investigators have noted a female predilection for the disease (54). PG has been reported rarely to develop after treatment with granulocyte colony-stimulating factor (G-CSF) and isotretinoin (55, 56).

Powell et al. (54) distinguish four variants within the clinical spectrum of PG: ulcerative, pustular, bullous, and vegetative forms. According to this schema, the ulcerative variant is typically associated with arthritis and IBD, the pustular variant with acute IBD, and the bullous variant with myeloproliferative disorders (57). The vegetative form has no specific association. Although this schema is useful, there is often overlap between the different forms.

A recent retrospective study of 86 patients with PG treated at two medical centers compared the clinical findings in patients with typical PG and patients with atypical PG (1). Patients who presented with hemorrhagic bullae that ulcerated and who had more superficial findings on skin biopsy were considered to have atypical PG (APG). Among patients with typical PG, three out of four had involvement of the legs. Only one of 64 patients (1.5%) had head and neck involvement. Among patients with APG, 77% had upper extremity involvement, frequently on the dorsal aspect of the hands. Of the 22 patients with APG, 10 (46%) were associated with an underlying condition usually considered a PG-associated disease. Hematologic malignancy or disease was also associated with APG in six patients (27.3%) as compared to 10.9% of typical PG cases.

Patients acutely ill with ulcerative colitis may develop fever and a sterile pustular eruption reminiscent of the skin lesions of gonococcemia (58). The pustules usually heal without scarring, but on occasion progress to typical PG ulcerations that heal with atrophic scars.

Diagnosis

Since there are no specific serologic or histologic markers for PG, diagnosis is based on the clinical presentation (16, 54). When painful, destructive ulcers with purple-red overhanging borders occur on the legs in the context of IBD, the diagnosis is usually straightforward. Ulcers in other areas, such as those appearing on the face, scalp or neck, may be more problematic. Head and neck involvement, when it occurs, is usually accompanied by lesions involving more characteristic sites (e.g., the anterior legs), but in some cases involvement is limited to the face, scalp and/or neck (59, 60). Although activity of PG may parallel that of active ulcerative colitis and has in fact been used as indication for colectomy, there is evidence that PG can occur during periods of remission, even by as much as 12 years after colectomy (61). Talansky et al. (6) studied 9 patients with PG who underwent intestinal resection for IBD. Two patterns of postoperative PG healing were noted: (a) prompt healing in 5 patients with moderate or severe IBD and (b) persistent disease requiring immunosuppressive treatment in patients with mild IBD prior to surgery or persistent bowel disease postoperatively. In the series studied by Levitt et al. (62), of 13 patients who underwent 15 resection procedures, PG healed quickly in 6 cases, only with additional therapy in 4 cases, and belatedly or not at all in 5 cases. PG has been reported to begin years after total proctocolectomy for IBD (63).

Differential Diagnosis

Many conditions have been confused with PG, resulting in delayed diagnosis, inappropriate treatment and unnecessary surgery. The differential diagnosis depends on the stage and site of disease and whether an atypical form of PG is present (Table 2). Early lesions of classical PG may present as an inflammatory pustule or nodule and might suggest folliculitis, gonococcemia, furunculosis, inflamed epidermal cyst, erythema nodosum, erythema induratum, vasculitis or thrombophlebitis. When an inflammatory ulcer is present, the differential diagnosis includes a variety of infections, vascular ulcers, neoplasms and reactions to ingested or external agents. Infections that may be confused

TABLE 2

Differential Diagnoses of Pyoderma Gangrenosum

Early Nonulcerated Pyoderma Gangrenosum
- Folliculitis
- Furuncles
- Arthropod bites
- Streptococcal gangrene
- Erythema multiforme
- Necrotizing vasculitis

Late Ulcerated Pyoderma Gangrenosum
- Atypical mycobacteria
- Behçet's disease
- Brown recluse spider bite
- Circulatory insufficiency
- Cryptococcosis
- Cutaneous amebiasis
- Factitial
- Halogenoderma
- Meleney's ulcers
- North American blastomycosis
- Pyoderma vegetans
- Sporotrichosis
- Syphilitic gumma
- Systematic lupus erythematosus
- Thrombophlebitis with gangrene
- Ulcerative necrobiosis lipoidica diabeticorum
- Wegener's granulomatosis
- Wound infection

Adapted in part from Keltz M, Lebwohl M, Bishop S. Peristomial pyoderma gangrenosum. J Am Acad Dermatol 1992; 27:360–364 (7) (with permission).

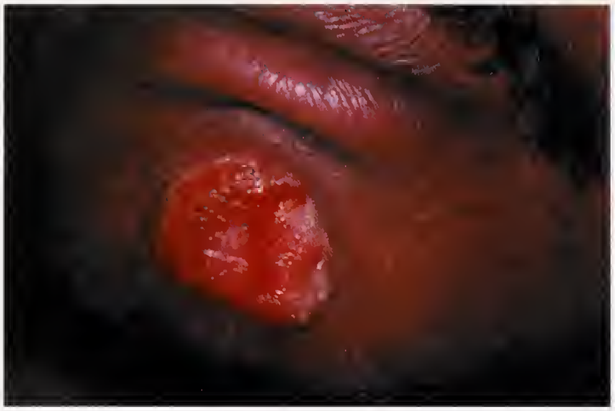

Fig. 5. Chronic ulcerative herpes simplex infection on the chin of a patient with AIDS.

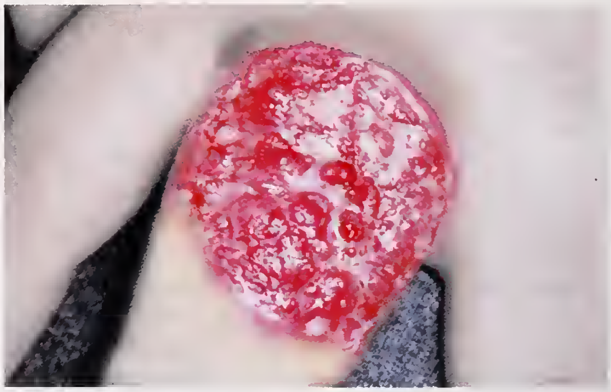

Fig. 7. Cutaneous leishmaniasis in a child who had visited Ecuador.

with PG include chronic ulcers of herpes simplex virus as seen with HIV infection (Fig. 5), bacterial pyodermas, blastomycosis-like pyoderma (Fig. 6), ecthyma gangrenosum, syphilitic gummas, cutaneous tuberculosis, atypical mycobacterial infections, deep fungal infections, leishmaniasis (Fig. 7) and cutaneous amebiasis.

Chronic vascular ulcers on the lower legs, common in older age groups, are exceptional in younger adults at risk for PG. Stigmata of venous insufficiency include varicosities, stasis dermatitis, pigmentary changes and chronic edema. Venous ulcerations usually occur near the medial malleolus and are rarely confused with PG. Arterial insufficiency generally produces ulcers that are painful on elevation. The extremity may be cool with shiny, hairless skin and decreased pulses. Vasculitic conditions such as polyarteritis nodosa, rheumatoid arthritis (Fig. 8), Wegener's granulomatosis, and Churg-Strauss syndrome can cause ulceration that could be confused with PG. Neuropathic ulcers occur in association with diabetes on weight-bearing surfaces.

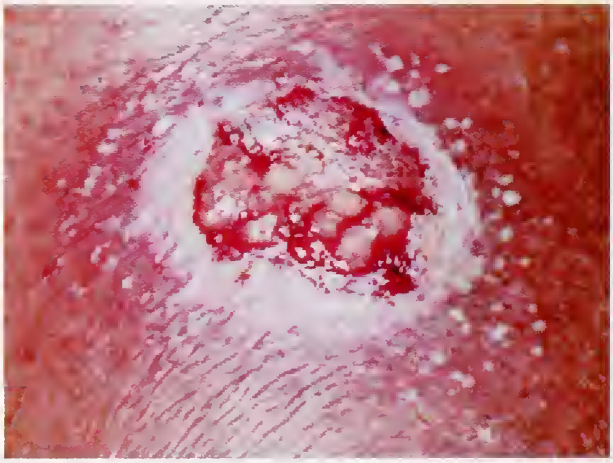

Fig. 6. Blastomycosis-like pyoderma (pyoderma vegetans) caused by *Pseudomonas aeruginosa*. Lesion healed completely with antibiotic therapy.

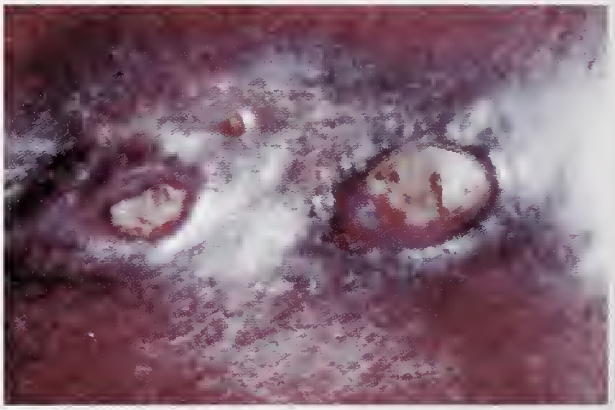

Fig. 8. Ulceration from rheumatoid vasculitis mimicking PG.

Certain drugs have been implicated as causes of PG and non-PG ulcerations. Isotretinoin and granulocyte-macrophage colony stimulating factor (GM-CSF) have been reported to cause PG, and ingestion of bromides or iodides may produce halogenoderma, a rare ulcerative condition resembling PG. Warfarin anticoagulants may induce painful necrotic lesions (Coumadin necrosis) in predisposed individuals, usually within the first five days of treatment (64).

We recently encountered an elderly woman with chronic lymphocytic leukemia who developed nonhealing, inflammatory ulceration of the legs several months after beginning hydroxyurea. There was no response to high-dose corticosteroids; in fact, she developed cellulitis after the initiation of cyclosporine. Such painful leg ulcerations have been described in the literature in patients receiving hydroxyurea for myeloproliferative disorders (65–73). It is thought that the selective cytotoxicity of hydroxyurea for cells that divide most actively (such as those of the skin) might cause these ulcerations by impairing normal wound healing in areas of trauma, especially if there is concomitant arterial or venous disease (65, 66). The impaired circulation of megaloblastic erythrocytes may also be of importance (68, 69).

Other rare conditions to be considered are brown recluse spider bite, syphilitic gumma, cutaneous blastomycosis, leishmaniasis and trigeminal trophic syndrome (74–78). Jemec and Konradsen (79) describe a case in which PG was mistaken for necrotizing fasciitis.

Once PG is suspected, certain laboratory studies should be obtained based on the clinical findings. These should include complete blood count, rheumatoid factor serology, antinuclear antibodies and an activated partial thromboplastin time (APPT). An elevated APPT might suggest the antiphospholipid antibody syndrome, which can cause cutaneous ulceration (80). Under certain circumstances, bone marrow examination, gastrointestinal studies, or HIV testing may be indicated. Because PG may occur prior to the onset of an associated disease, patients with PG should be re-evaluated periodically.

The role of biopsy in the work-up of patients with PG is controversial, because pathologic changes are not diagnostic and there is risk of a superimposed pathergic response and extension of the ulcer. However, it may be necessary to accept the added risk to exclude infection or vasculitis.

The histopathology of PG is nonspecific and varies according to stage, variant, and biopsy location (81, 82). Necrotizing, suppurative neutrophilic infiltration is prominent along with ulceration, and there may be evidence of leukocytoclasis. Frank vasculitis is rarely reported in areas of maximal tissue destruction, but the underlying process is probably not primarily a neutrophilic vasculitis (81, 82). In some cases, a necrotizing, pustular, neutrophilic, follicular reaction may be the central nidus of the lesion. PG is considered one of the neutrophilic dermatoses, which include leukocytoclastic vasculitis, Sweet's syndrome, Behçet's disease, erythema elevatum diutinum, rheumatoid neutrophilic dermatitis, and skin lesions of bowel bypass syndrome. Biopsy of the erythematous leading border may show a mononuclear infiltrate of lymphocytes, macrophages, plasma cells and mast cells (17). To aid in cases where an infectious etiology is suspected, culture and sensitivity of the biopsy specimens is advisable for bacteria, tuberculosis, atypical mycobacteria, and fungi.

Treatment

The treatment of PG depends on the extent, severity and chronicity of the lesions, previous treatment, underlying conditions and pertinent coexisting medical disease. Currently, there is no one definitive treatment regimen for PG. Local therapy alone is sometimes adequate to arrest smaller, early lesions, but systemic treatment is required for more severe disease (7, 54). We favor aggressive treatment to halt progression, decrease pain and prevent extensive scarring. Because PG is extremely painful, treatment should include adequate analgesia. Opiates are often necessary.

Local therapy includes topical wound care and sometimes topical and intralesional corticosteroids (19). Daily cleansing, antiseptic compresses and dressing changes are useful in avoiding wound superinfection. Triamcinolone acetonide 10–40 mg/mL injected into the base and borders of the lesion is sometimes helpful but should not be used in infected lesions (16, 83). Injections are painful and often not well tolerated. Topical anesthetics are of some value in decreasing the pain of injection, but to prevent excessive absorption and toxicity, they should be used cautiously on large wounds. Surgical debridement should be avoided, since it may cause extension of the ulcer and further tissue damage.

Aggressive, rapidly progressing lesions and/or lesions unresponsive to local measures require systemic therapy, usually with glucocorticoids (16, 83). In the last few years, cyclosporine has been found to be highly effective and is considered by some to be the treatment of choice for PG. Prior to the initiation of immunosuppressant therapy, infection should be excluded. If corticosteroids are used, large doses of prednisone, up to 120 mg daily, may be required to halt the rapid progression of the ulceration. Once the ulcer ceases to expand and the peripheral erythema fades, corticosteroids can be tapered slowly over a three-month period. Rapid withdrawal of prednisone may precipitate reactivation of PG and should be avoided. Corticosteroid pulse therapy using suprapharmacologic doses of corticosteroids has been reported to be effective in patients with severe PG (84, 85). Patients must be carefully monitored for cardiac arrhythmias and electrolyte abnormalities (86). Recently, in a recalcitrant case, pulse methylprednisolone was used in combination with cyclosporine (60).

Dapsone, a sulfone used for a variety of infectious and inflammatory diseases, is reported to be helpful in the treatment of PG. Its main advantage is that it allows reduction in corticosteroid dosage. Although dapsone is used safely worldwide with minimal toxicity for the treatment of leprosy, there are some well-established toxic effects. Blood dyscrasias, including hemolysis, methemoglobinemia, leukopenia and rarely agranulocytosis, have been reported (87). Most patients on dapsone will develop some hemolysis and mild anemia, but in patients with a deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD), the anemia may be more profound and life threatening. This is especially relevant in patients with underlying cardiovascular disease. Pretreatment measurement of this enzyme is recommended in high-risk groups. Agranulocytosis, though rare, is life threatening. Along with low white blood cell count, it presents with sore throat, fever and sometimes a morbilliform eruption. Other adverse effects of dapsone include toxic hepatitis, renal disease, drug hypersensitivity syndrome and neuropathy, as well as gastrointestinal side effects.

Cyclosporine, a highly potent immunosuppressant agent used in transplantation patients, has recently been found to be effective in the treatment of refractory and severe cases of PG (88 – 92). The drug prolongs allograft survival by suppressing T-lymphocytes and lymphokines (89). An advantage of cyclosporine over other immunosuppressants is the absence of bone marrow suppression (83). Most PG patients respond to low doses of cyclosporine, ranging from 3 – 6 mg/kg per 24 hours (83, 88 – 90). Patients receiving cyclosporine should be carefully monitored for blood pressure elevation and deterioration of renal function. In addition, liver functions and triglycerides should be evaluated periodically. Other side effects associated with high doses of cyclosporine include anaphylaxis, hyperkalemia, and hyperuricemia. Cyclosporine should only be administered by physicians experienced in its use.

Mycophenolate mofetil has been used to improve the efficacy of cyclosporine in particularly recalcitrant cases of PG (93, 94). It is usually administered in doses of 1 g twice daily. Reported side effects include abdominal cramps, nausea, vomiting, diarrhea, mild-to-moderate leukopenia, and anemia and liver function abnormalities. As with any immunosuppression, patients should be advised of the potential for the development of lymphoma, although the incidence of this complication is not known.

Systemic tacrolimus (FK-506) and tacrolimus ointment alone or in combination with systemic tacrolimus or cyclosporine have been effective in treating PG (95 – 97).

Thalidomide has been used successfully in the treatment of PG (10, 98, 99). Because of severe teratogenicity, it should not be administered to women who might become pregnant. Side effects of thalidomide include a sensory peripheral neuropathy, drowsiness and constipation (100). Other treatments that have been reported anecdotally to benefit patients with PG are transdermal nicotine, subcutaneous and perilesional GM-CSF, minocycline, clofazimine and chlorambucil (101 – 105). A recent case report of PG associated with ulcerative colitis and arthritis was attributed to margination of neutrophils from increased adherence of neutrophils to vascular endothelium (106); the patient had a rapid response to intravenous heparin.

If an associated systemic disease is present, it should be treated aggressively. Occasionally, successful chemotherapy of leukemia and other myeloproliferative disease may cure PG (107). In some patients with ulcerative colitis, resection of the affected colon was followed by healing of the skin lesions. However, the correlation between associated disease activity and skin disease progression is variable, and colectomy usually is not indicated merely for treatment of PG.

The prognosis of PG is variable. Depending on the initial severity of the ulcer and choice of treatment, healing occurs in weeks to months and, in some cases, may take up to a year (6). PG may recur upon withdrawal of steroids or immunosuppressive agents. Chronic treatment may sometimes be necessary.

Summary

PG is an uncommon clinical condition whose pathophysiology remains poorly understood. It is often painful, and because of rapid spread and extensive tissue destruction, requires immediate, aggressive treatment. The presence of PG is frequently an indication of concomitant serious medical illness, most commonly IBD. These illnesses should be treated by the appropriate medical specialist.

The differential diagnosis of PG must include cutaneous infections, vascular disorders and malignancy. Clues to the diagnosis of PG include a violaceous overhanging edge with tender surrounding erythema, a granular purulent base and the ability to express pus. Because the treatment of PG often requires immunosuppressive agents that can exacerbate infection, it is essential to make a correct diagnosis prior to initiating therapy. Infection should be ruled out, or if present, treated aggressively with antibiotics. Appropriate medication should be given to alleviate pain. Patients should be monitored carefully to avoid adverse effects of treatment and drug interactions.

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Evaluation and Treatment of Itching in HIV-Infected Patients

Joel M. Gelfand, M.D., and Donald Rudikoff, M.D.

Abstract

Itching is a common complaint among patients infected with HIV and may cause significant morbidity and embarrassment. Although idiopathic HIV-pruritus has been described, it is probably less common than was previously thought. In most patients, a careful history and physical examination will show that a dermatosis accounts for their pruritus. Dry skin, seborrheic dermatitis, eczema, psoriasis, pruritic papular eruption, staphylococcal folliculitis and prurigo nodularis are frequently encountered in these patients. These common dermatoses, drug eruptions, several rarer conditions and systemic causes of itching should be excluded before diagnosing idiopathic HIV-pruritus. Treatment should be directed to the underlying skin problem and may be supplemented with sedating antihistamines. Phototherapy is a safe and effective therapeutic modality for many pruritic dermatoses as well as for idiopathic pruritus.

Key Words: Itching, pruritus, HIV.

Itching, a common symptom in HIV-infected patients, can cause embarrassment, discomfort and sleep loss. It may be a presenting symptom of a number of HIV- or non-HIV-associated dermatoses or may occur without any visible eruption (1). Chronic itching and scratching often result in lichenification, excoriation, prurigo nodularis, pigmentary alteration and secondary infection.

Although the pathophysiology of itching is poorly understood, it is thought to result from local skin changes or, in some cases, from a central mechanism possibly related to circulating pruritogens. A number of chemical mediators, including histamine, serotonin, prostaglandins, cytokines, proteases, tachykinins (e.g., substance P), and opioid peptides are thought to be involved on a local level (2). HIV-infected patients frequently display xerosis, i.e., dry skin, which might have some physiochemical effect on "itch fibers." Recently, Schmelz et al. identified histamine-sensitive C-fibers, which have particularly thin axons but excessive terminal branching that may represent the afferent units mediating the itch sensation (3).

In patients infected with HIV, pruritus can develop as a consequence of routine "itchy" dermatoses, some of which may be exacerbated or may occur more frequently in the setting of HIV infection. These dermatoses include papulosquamous disorders, skin infestations or infections, and drug reactions. Drug eruptions are particularly common because of abnormal immunoreactivity, altered drug metabolism and polypharmacy. Moreover, itching may be associated with systemic diseases, such as renal failure or liver disease, or it may be a manifestation of progressive immunodeficiency and dermatoses peculiar to HIV infection.

Evaluation of the HIV patient with pruritus should include a complete skin and physical exam, and laboratory tests as indicated by the history and clinical presentation. Moreover, the patient's CD4 count and viral level, as measured by polymerase chain reaction (PCR), may also be useful. Optimum anti-viral therapy should be instituted, since this not only slows the progression of HIV infection and increases life expectancy, but also has been reported to reverse certain HIV-related skin disorders (4).

Xerosis

Generalized asteatosis, often referred to as "xerosis" or "dry skin," is a common finding in HIV-infected patients. It becomes more severe with disease progression as CD4 counts decline. Characteristically, the skin appears rough and lusterless, often with fine scale, best appreciated under tangential lighting. Xerosis is particularly

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prominent on the extremities and is exacerbated in winter months. Alterations in skin hydration and barrier function predispose to irritant dermatitis, pruritus, excoriation and secondary infection. Treatment includes avoidance of harsh soaps and hot water. Emollients should be applied in the first few minutes after bathing, while the skin is still moist. In general the greasier emollients are preferred, but these too may be unacceptable to many patients. Mild, oilated soaps or soap substitutes are recommended.

Idiopathic Pruritus

Idiopathic pruritus similar to that found in Hodgkin's disease has been described in patients with advanced HIV infection (5, 6). Because such patients often have dry skin, a known cause of itching, some authors think idiopathic pruritus is uncommon. Before attributing itching to idiopathic HIV pruritus, a primary dermatological diagnosis should be sought. Subtle manifestations of scabies, xerosis, atopic dermatitis, and papular eruption of HIV should be eliminated, as should systemic disorders such as renal failure and liver disease, before this diagnosis can be made.

Oral antihistamines are of limited benefit. The authors sometimes use sedating antihistamines if the patient has trouble sleeping through the night. It is critical to be aware of drug interactions when using astemizole. Protease inhibitors and anti-fungals such as itraconazole, which are often used to treat HIV-infected patients, inhibit cytochrome P450 enzymes and can lead to fatal arrhythmias if used in conjunction with astemizole or cisapride (7). We have found doxepin, a tricyclic antidepressant with antihistaminic properties, to be particularly useful. It should be used with care in the presence of heart disease, and is contraindicated if there is coexistent narrow-angle glaucoma or prostatic hypertrophy.

Several studies have shown that ultraviolet B (UVB) phototherapy is helpful for the treatment of HIV-associated pruritus. The itching generally diminishes after 4–8 weeks of treatment. Although ultraviolet exposure can theoretically increase HIV replication, we have found no adverse effect of UVB phototherapy on HIV patients' plasma viral levels as measured by quantitative PCR (8). The overall experience of UVB phototherapy in HIV-positive patients suggests that this is a safe modality (9). Caution should be observed with patients presenting cutaneous evidence of Kaposi's sarcoma. Psoralens plus long-wave ultraviolet light (PUVA) have also been reported to be beneficial in the treatment of idiopathic pruritus (10).

Pentoxifylline and indomethacin have recently been reported to be effective in relieving HIV-related pruritus, although this has not been confirmed in randomized, controlled studies (11, 12).

Pruritic Papular Eruptions

Several chronically itchy papular and papulopustular eruptions, variously referred to as pruritic papular eruption (PPE) of HIV infection, "itchy red bump disease," eosinophilic pustular folliculitis, eosinophilic folliculitis (EF), papular urticaria, prurigo nodularis and insect bite reactions, have been reported in HIV-infected patients. PPE probably represents a heterogeneous spectrum of papular and papulopustular skin eruptions with similar or overlapping clinical and histological features and response to therapy (13). It has been reported in series from Africa, Haiti, Brazil and the United States (14–16). In the Haitian study (16), PPE was seen in 46% of patients with AIDS and was the presenting manifestation in 79%, often appearing months before the diagnosis of an AIDS-defining condition. PPE, and more specifically EF, is seen in the context of deterioration in the immunity of HIV patients. Patients consistently have CD4 counts below 200 (17, 18). In one study, 81.25% had CD4 counts less than 100, and 75% had CD4 counts below 50 (19). Some investigators have noted a decrease in EF prevalence with the advent of aggressive antiretroviral treatment, although the immune reconstitution accompanying such treatment can sometimes cause a flare-up of EF.

PPE presents as erythematous urticarial papules resembling arthropod bites (Fig. 1). There may be pustules or papules surmounted by pustules, but in our experience the lesions are mostly excoriated. Lesions are typically found on the extremities and trunk, with sparing of the palms, soles and digital web spaces (13). Patients frequently have prurigo nodules if the condition is longstanding. Lichenified patches and plaques on the arms and legs may be seen, probably representing an AIDS-associated, late-onset, atopic dermatitis.

Histopathologic exam in PPE reveals hyperkeratosis, acanthosis, focal dyskeratotic and necrotic cells in the epidermis, and dermal fibrosis with proliferation of factor XIIIa-positive dermal dendrocytes. The dermal infiltrate also includes lymphocytes, plasma cells, eosinophil and mast cells.

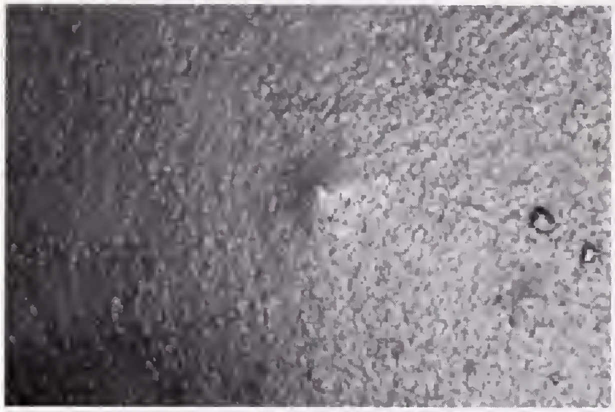

Fig. 1. Pruritic papular eruption: papule surmounted by pustule.

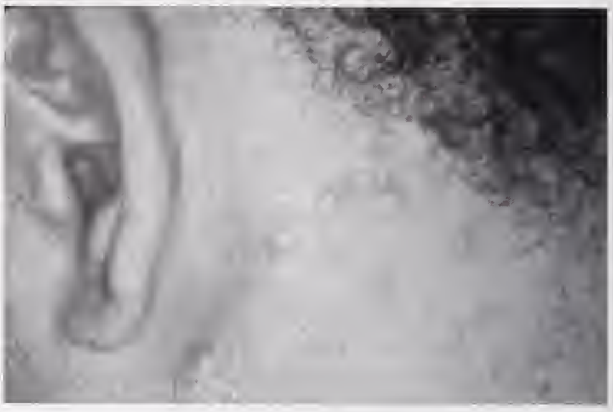

Fig. 3. Post-auricular lesions of eosinophilic folliculitis.

PPE follows a chronic waxing and waning course, and may have an associated peripheral eosinophilia and elevated levels of IgE. Sanchez et al. evaluated 41 patients with HIV-associated pruritic eruptions (20). They found that 80 percent had CD4 T-cell counts below 100 cell/mm^3, 77% had elevated IgE levels, and 55% had elevated eosinophil counts. The pruritus is typically not relieved by antihistamines or topical treatment, but UVB phototherapy is usually effective. Ultra-potent topical corticosteroid ointments may be of some benefit.

Eosinophilic folliculitis (EF) presents as erythematous urticarial papules, pustules, and/or papules with pinpoint vesicles or pustules on the face, neck, upper chest and back, characteristically above the nipple line (Fig. 2). The upper arms, eyelids, post-auricular areas and scalp are often involved (Figs. 3, 4) (21). More extensive involvement of the forearms, thighs and trunk below the nipples is less common. Pruritus is usually severe and unrelieved by antihistamines, and tends to be chronic with occasional periods of remission. Laboratory examination may reveal elevated IgE levels and peripheral eosinophilia.

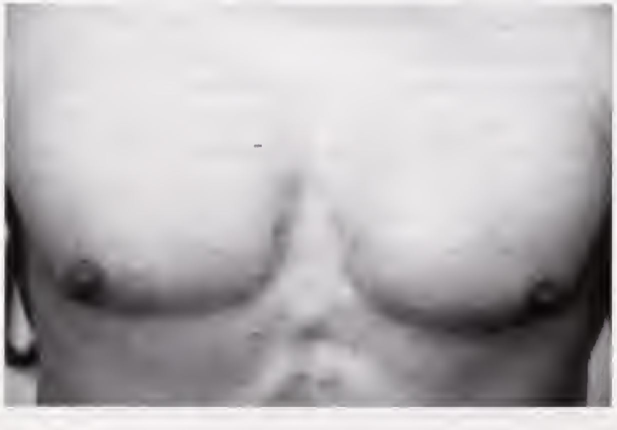

Fig. 2. Lesions of eosinophilic folliculitis on upper chest.

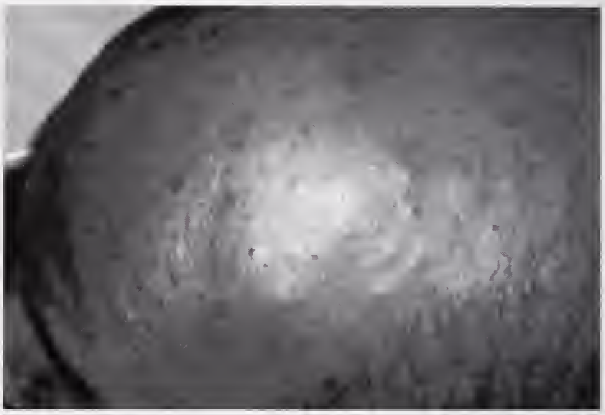

Fig. 4. Eosinophilic folliculitis: scalp involvement.

Histopathologic examination reveals follicular spongiosis and folliculocentric inflammatory infiltrates involving the outer root sheaths of hair follicles. The infiltrate is rich in eosinophils but also contains lymphocytes, histiocytes, neutrophils and mast cells (21, 22). Eosinophilic abscesses and flame figures may be seen. Magro and Crowson found significant coating of perifollicular mononuclear cells with IgE in two HIV-infected patients, a situation analogous to lesional skin of patients with atopic dermatitis (23). A simple method of diagnosing EF which correlates well with biopsy diagnosis is to prepare a smear from an intact pustule if one can be found. Staining with Wright's stain will reveal a predominance of eosinophils (18). A recent study demonstrated that sectioning biopsies horizontally rather than vertically may be helpful in diagnosing EF (24).

Also within the spectrum of PPE are papular eruptions that resemble "insect bite reactions" or papular urticaria, an entity usually seen in immunocompetent children who have had flea or bed bug bites. Some authors feel that if enough sections are studied, eosinophilic folliculitis will be found. Studying 7 patients with such reactions, Penneys et al. demonstrated increased levels of circulating antibodies to antigens found in salivary glands removed from the salt marsh mosquito, *Aedes taeniorhynchus* (25). These authors ascribed the eruption to chronic recall reactions at previous mosquito bite sites.

There is an overlap not only in the clinical presentations of papular eruptions of HIV but also in different responses to therapy; however, there have been no randomized, controlled trials to date to validate the variety of reported treatments. Eosinophilic folliculitis frequently responds to UVB phototherapy and isotretinoin (8, 26, 27). There are reports that EF may also improve with cetirizine, itraconazole, metronidazole, ivermectin and long-term application of permethrin, the latter two implying a possible role for Demodex mites in the pathogenesis (28–32). In our experience, papular urticaria-like eruptions are often resistant to treatment and although systemic corticosteroids may be efficacious, their long-term use could be problematic in HIV-infected patients. Some investigators use periodic, tapering doses of steroids.

Prurigo nodularis, usually resistant to most therapeutic modalities, sometimes responds to phototherapy and intralesional steroid injections. There is a recent report that thalidomide may be useful, implying a possible immune or neurogenic pathogenesis for this condition (33). Some authors have suggested a mycobacterial causation of prurigo nodularis, but it is likely that the presence of mycobacterial DNA in these lesions, detected by PCR, is a result of secondary invasion of ambient microorganisms caused by scratching (34).

Papular mucinosis, an unusual, sometimes pruritic eruption caused by the deposition of mucin in the dermis, has been reported in patients with HIV infection (35). The eruption, sometimes referred to as lichen myxedematosus, is usually associated with an IgG paraproteinemia. A minority of cases reported in association with HIV infection have been pruritic. We have recently encountered a male patient with lichen myxedematosus with extremely itchy papules on the posterior aspect of the neck and the upper back (Fig. 5). He had no paraproteinemia. In fact, most of the cases reported in association with HIV infection have lacked this feature.

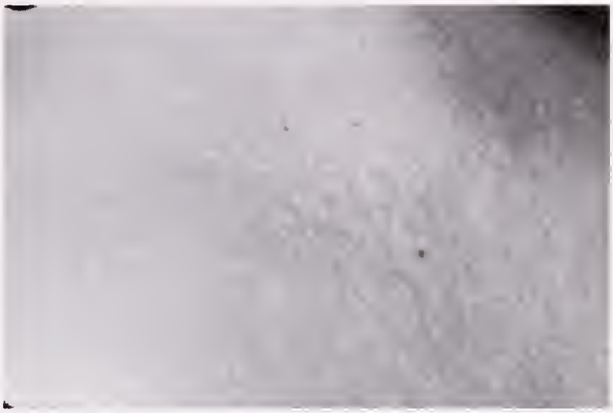

Fig. 5. Papular mucinosis with cobblestone appearance on upper back.

The pathophysiology of papular eruptions is not completely understood, but has been attributed in part to immune dysregulation with abnormal host responses to such infectious agents as staphylococci, saprophytes such as Demodex mites, or Pityrosporum yeasts (36). An immune reaction to antigens in the saliva of biting insects or an autoimmune reaction to a component of sebum has also been postulated (25, 37). There is evidence that a shift toward a Type-2 cytokine profile may be important in eosinophilic folliculitis (38). This is based on recent evidence that Type-2 responses may predominate in late-stage HIV disease, the known loss of delayed-type hypersensitivity (DTH) with AIDS, and the likelihood that IL5 from type-2 cytokine producing cells could attract eosinophils into the lesional skin.

The possibility of immune dysregulation in HIV-related papular eruptions is supported by data that many patients with late-stage disease have elevated eosinophil counts that in most cases correlated with skin diseases such as eosinophilic folliculitis, atopic dermatitis and prurigo nodularis (39). There is a rise in circulating levels of eosinophilic cationic protein (ECP) in both atopic and non-atopic HIV patients (40).

Moreover, there is evidence that pruritic papular eruptions occur in non-HIV-infected patients with immune dysfunction, suggesting that the disturbance of immune function is of paramount importance. PPE has been reported in the syndrome of idiopathic CD4+ lymphocytopenia, and eosinophilic folliculitis has been reported in a patient with Waldenström's macroglobulinemia and in patients immunosuppressed after high-dose chemotherapy and bone marrow engraftment for non-Hodgkin's lymphoma (41, 42). Recently, data was presented supporting a Type-2 cytokine shift in eosinophilic folliculitis and an important role for the chemokine eotaxin (43–46).

Photodermatitis

Photosensitivity has been described in HIV-infected patients with advanced immunodeficiency, sometimes in the absence of other disease manifestations (47). It is thought to be related to a photosensitizing drug in most cases. Chronic lichenoid photoeruptions (Figs. 6, 7) with severe pruritus and violaceous plaques on the dorsa of the hands, forearms, face and neck were described by Berger and Dhar in patients with severe immune suppression (helper T-cell count under 50 cells per cubic milliliter) (48).

Afro-American patients were disproportionately affected; pigmentary alterations, especially hyperpigmentation, but also hypopigmentation, were prominent. Treatment includes avoidance of sun exposure, use of topical sunblocks that block UVA and UVB, and in some instances, photochemotherapy (psoralen plus UVA or PUVA) or etretinate (49).

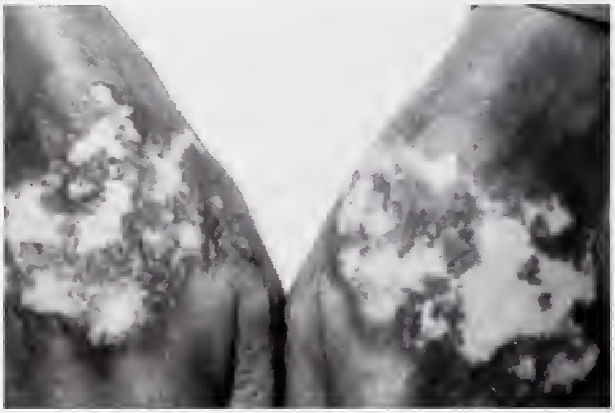

Fig. 6. Lichenoid photodermatitis: hyperpigmented plaques with central depigmentation on sun- exposed skin of the hands.

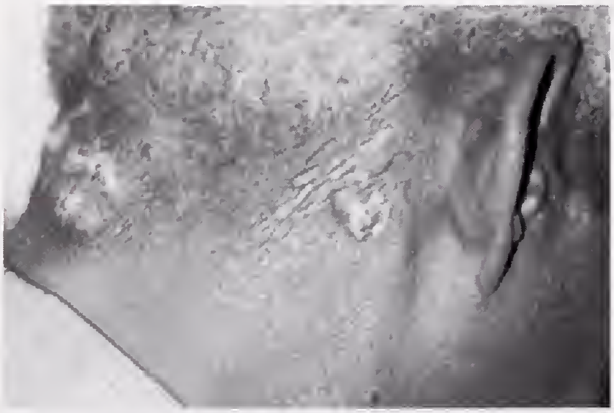

Fig. 7. Lichenoid photodermatitis: hyperpigmentation on sun-exposed skin of posterior neck and ears associated with several lichenoid plaques.

Papulosquamous Disorders Exacerbated by HIV

Psoriasis

Psoriasis occurs with approximately the same frequency (about 1%) in HIV-infected patients as in patients who are not infected (50). It is frequently itchy for both groups of patients. The condition may be exacerbated by underlying HIV infection, is more difficult to treat than non-HIV-related psoriasis, and may become worse as patients progress to AIDS (51, 52). A significant proportion of patients with HIV-associated psoriasis have a pattern of acral involvement, often with pustules and sometimes with severe, destructive nail changes (Fig. 8) (50). Psoriasis in HIV-infected patients may respond to the usual measures, such as topical corticosteroids, calcipotriol or tazarotene for localized disease and PUVA or UVB phototherapy for more extensive involvement. In addition, antiretroviral therapy is often associated with an improvement in psoriasis (52, 53). A recent survey found that phototherapy is widely used for HIV-infected patients: 80% received UVB, 9% received PUVA and the remaining 11% received a variety of combination and other therapies (54). A case has been made that PUVA may be preferable to UVB therapy because of its increased efficacy, especially with thick plaques and palmoplantar involvement, as is frequently encountered in the setting of HIV-associated psoriasis (55). As with UVB, PUVA may also theoretically activate HIV replication; however, pilot studies have found no evidence of increased HIV activity in HIV patients treated with PUVA (56, 57). Nevertheless, PUVA may not be preferable in HIV patients, due to the gastrointestinal side effects of psoralens and the

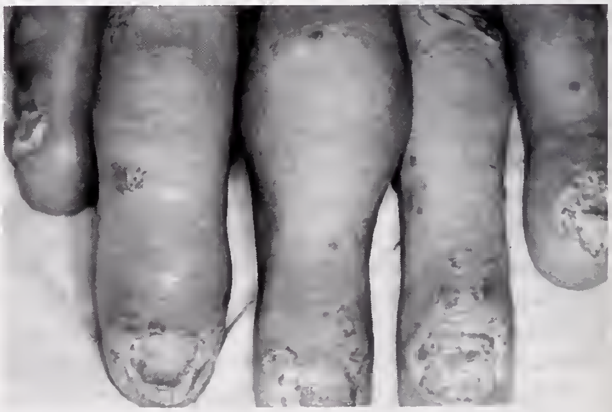

Fig. 8. Acral psoriasis, psoriatic arthritis and destructive nail changes.

potential for carcinogenesis, which may be exacerbated by the immunosuppressed status of these patients. Systemic retinoids such as etretinate or acitretin have been particularly useful for treatment of generalized psoriasis. Methotrexate has been reported to cause profound leukopenia and death in some psoriatic patients with HIV infection and is avoided by many practitioners (49). However, in a recent report, there was no clear deterioration with methotrexate use for AIDS-associated psoriatic arthritis (58). Because of the known interaction with sulfamethoxazole-trimethoprim, methotrexate should not be used in patients receiving this drug for prophylaxis against *Pneumocystis carinii*.

Eczema/Atopic Dermatitis

Although there are no prospective studies of the effect of HIV infection on atopic dermatitis, eczematous dermatitis has been described in both pediatric and adult patients with HIV infection as well as HIV-infected hemophiliacs (59). A recent survey of atopic manifestations in HIV-infected patients found chronic pruritic rashes or eczema in 29% of patients (60). Family history of asthma or hay fever was significantly associated with chronic pruritic rashes and eczema. There is a report of a 40-year-old male AIDS patient who developed atopic dermatitis after treatment with AL721, a mixture of egg yolk lipids used in the past in the treatment of AIDS (61).

Seborrheic Dermatitis

Seborrheic dermatitis may be a marker for early HIV disease (CD4 counts > 500). HIV-infected patients often have extensive involvement, with redness and scaling of the central face and scalp (Fig. 9). The pathophysiology is unclear but is thought possibly to be related to an inflammatory response to the yeast *Pityrosporum ovale*. Because tinea infections such as tinea faciei (Fig. 10) may occur in this patient population and mimic seborrheic dermatitis, a potassium hydroxide examination for hyphae should be performed if the diagnosis is in doubt (62). Treatment includes shampoos with coal tar, selenium sulfide, ketoconazole or pyrithione zinc and creams containing mild corticosteroids or ketoconazole.

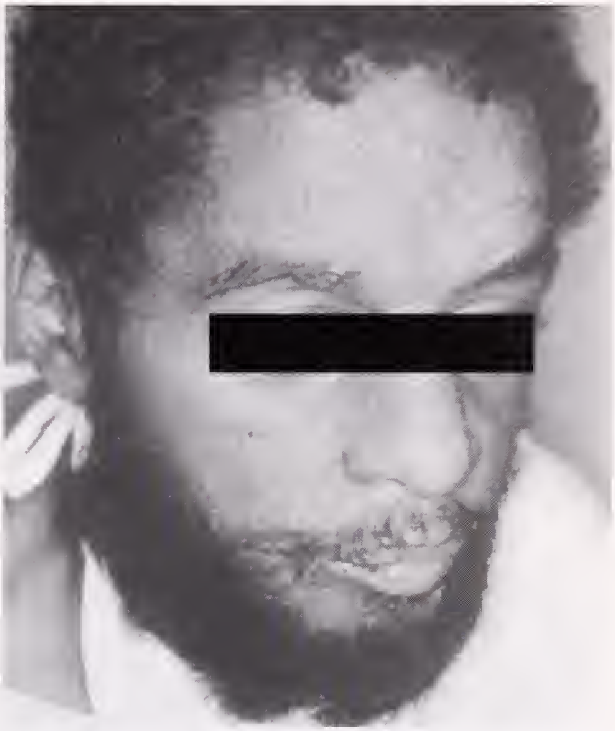
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Fig. 9. HIV-associated seborrheic dermatitis with extensive scaling.

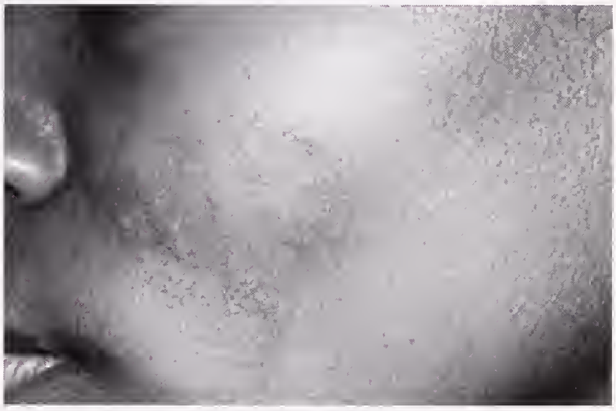
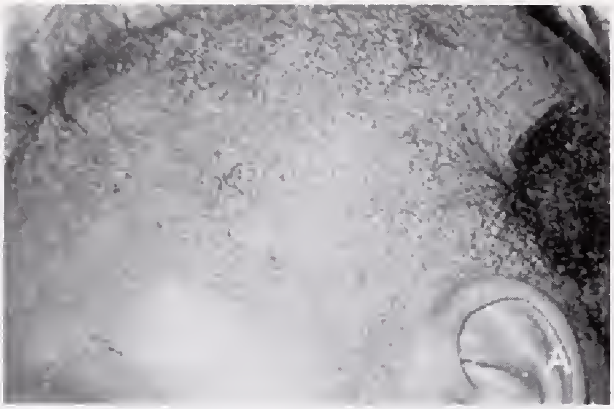


Fig. 10. Annular lesions of tinea faciei.

Skin Infections/Infestations

Fungal (Tinea, Candida)

Cutaneous fungal infection with dermatophytes (tinea infection) is common in patients infected with HIV. One study found a 37.3% colonization rate among HIV-infected homosexual males compared to a 31.8% rate among non-HIV-infected homosexual male controls (63). As with psoriasis, the prevalence of tinea infection may not be greater in HIV-infected individuals; however, the infection may be exacerbated by immunodeficiency. We have encountered a number of HIV-infected patients with extensive tinea infections, including tinea capitis (Fig. 11A), faciei, corporis (Fig. 11B), cruris, pedis and manuum. In addition, tinea infections in this patient population may be more resistant to treatment. Treat-



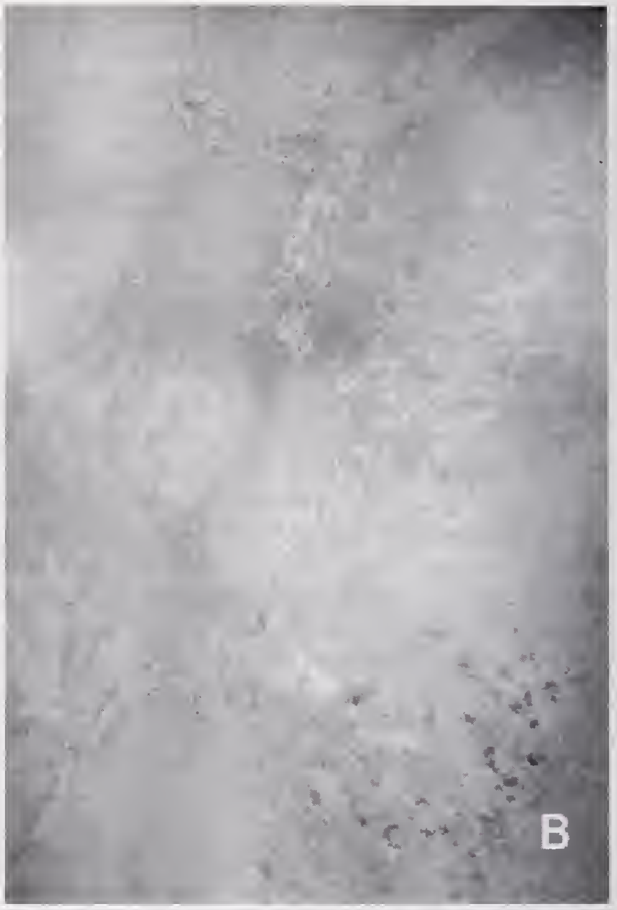


Fig. 11. **A.** Tinea capitis: "black dot ringworm" in HIV-infected adult patient. **B.** Tinea corporis with extensive scaling of the trunk. (A and B represent the same patient.)

ment includes topical antifungal agents, and in more severe cases systemic antifungal agents such as fluconazole, itraconazole or terbinafine. The absorption of itraconazole requires an acid pH in the stomach and may be impaired in some patients with HIV infection. Certain drugs such as didanosine (DDI) can interfere with the absorption of itraconazole (64).

Bacterial Folliculitis

Staphylococcus aureus folliculitis is a common cutaneous infection in HIV-infected patients. Duvic described a pruritic intertriginous or axillary eruption in HIV-infected patients, with confluent red lesions and satellite pustulosis resembling cutaneous candidiasis (Fig. 12) (5). The high prevalence of staphylococcal skin infections in HIV-positive patients may be due in part to high staphylococcal nasal carriage rates in these patients, i.e., twice that of controls (65). Although carriage rates were increased over controls in hospitalized HIV-infected patients in one study, another study found no independent association between HIV status and staphylococcal nasal colonization in outpatient drug users (66). This study did find inhalational drug use to be independently associated with nasal carriage of staphylococci. Mupirocin ointment applied intranasally eradicated staphylococci for several weeks in HIV-infected patients but the effect waned over time, with persistently negative cultures of 63%, 45% and 29%, at 2, 6, and 10 weeks respectively (67).

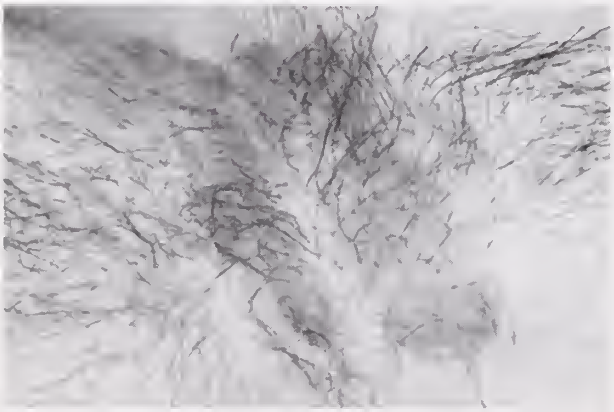


Fig. 12. Staphylococcal-infected dermatitis of the axilla.

A chronic recalcitrant "toxic-shock-like" disorder has been described in HIV-infected patients (68). Staphylococci may also superinfect molluscum contagiosum lesions and lead to symptoms of pruritus. Treatment of staphylococcal infections includes oral antibiotics such as dicloxacillin, chlorhexidine gluconate (Hibiclens) washes and topical mupirocin.

HIV-infected patients occasionally suffer infestations with scabies and pediculosis. Atypical presentations including crusted scabies (Fig. 13) have been reported in this population. Patients with crusted (Norwegian) sca-

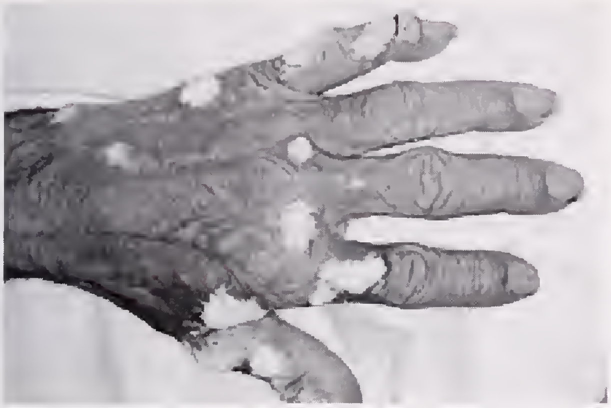


Fig. 13. Hyperkeratotic lesions of crusted scabies.

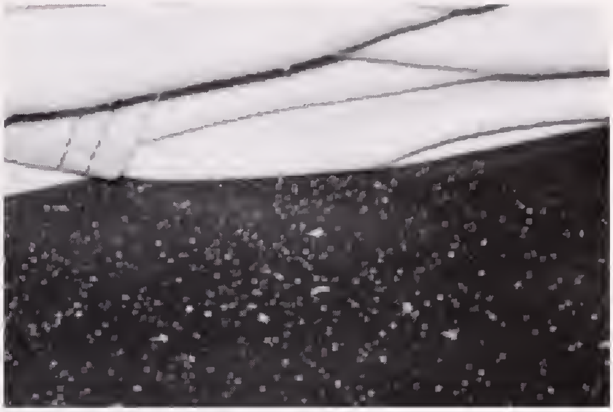


Fig. 15. Flaking on exam table from patient with crusted scabies and psoriasis.

bies often present with a generalized papular, crusted and scaly eruption. The scale is typically a "dirty" gray or brown. There may be involvement of the neck, scalp and beard area (Figs. 14A, 14B). We have recently seen a patient with coexistent psoriasis and crusted scabies (Fig. 14C). After two weeks of topical treatment he returned and was still shedding scales (Fig. 15), which demonstrated scabies mites (Fig. 16). This underscores the contagiousness of this condition and the need for isolation of such patients until they are adequately treated and deemed noninfectious. Scabies may also cause papular urticaria with erythematous papules noted on the extremities. Treatment of crusted scabies consists of keratolytics to remove scales and the application of scabicides such as permethrin, lindane or malathion lotion. Recently ivermectin, a drug used for onchocerciasis, has been found to be effective in the treatment of crusted scabies in HIV-infected patients. The dose is 200 g/kg given once followed by a second dose one week later. Family members should be treated, as should fomites. Pediculosis pubis may also be seen in HIV-infected patients. Infestation may also occur on the eyelids or on the trunk in hairy individuals (Figs. 17A, 17B).

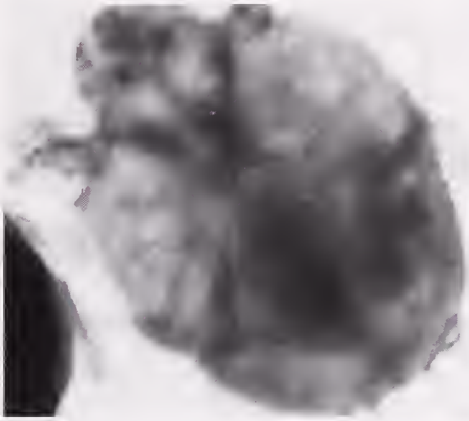


Fig. 16. Scabies mite from exfoliated scale.

Systemic Disease

Systemic causes of pruritus in HIV-infected patients (other than HIV infection itself) are relatively uncommon (69). They include chronic renal failure as a result of HIV nephropathy, hepatic failure as a result of co-infection with hepatitis B or C, and systemic lymphoma. Drug eruptions are common in the setting of HIV infection and may cause severe pruritus. Moreover, dermatographism may be a cause of itching in

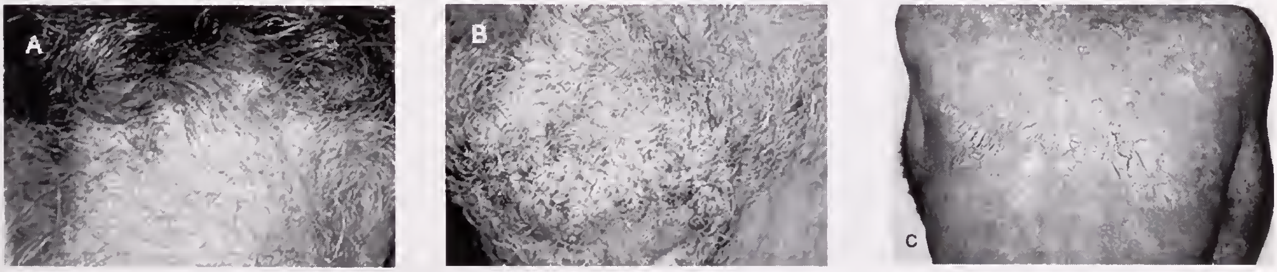


Fig. 14. A. Crusted scabies on posterior neck and scalp. **B.** Crusted scabies of the beard area. **C.** Crusted scabies in patient with extensive psoriasis. (A, B and C represent the same patient.)

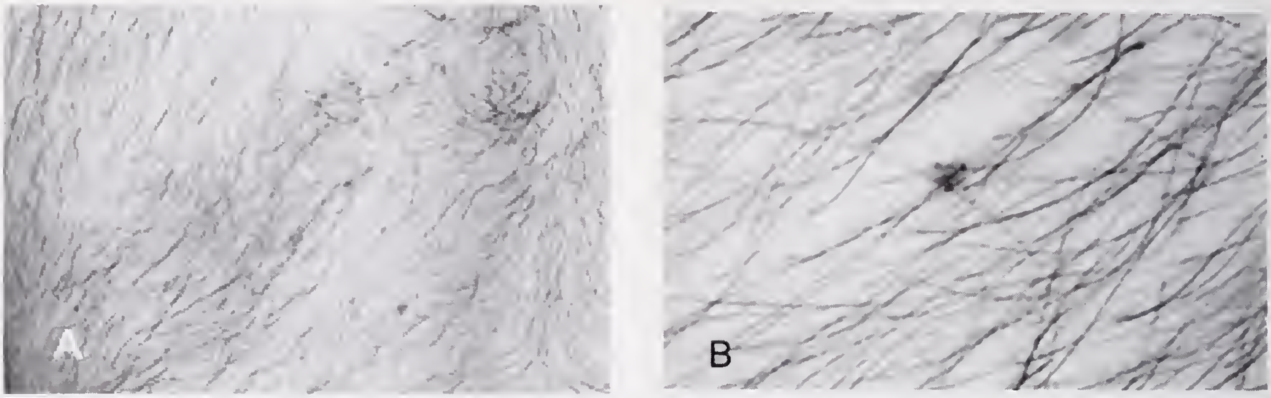


Fig. 17. **A.** Erythematous area on the back of HIV-infected patient with pruritus. **B.** Closer examination reveals crab louse.

some patients (Fig. 18). Work-up of systemic causes of pruritus includes a history and physical examination, complete blood count, liver and kidney function tests, hepatitis serologies, and chest X-ray. The presence of jaundice, lymphadenopathy, hepatosplenomegaly, or subtle signs of hyper- or hypothyroidism should direct further testing.

Conclusion

Pruritus is an important cause of discomfort and morbidity in patients infected with the human immunodeficiency virus. Work-up should include a careful skin examination to rule out a primary dermatologic etiology before attributing itching to idiopathic HIV pruritus. If no dermatologic cause is found, a systemic cause or medication-related etiology should be sought.

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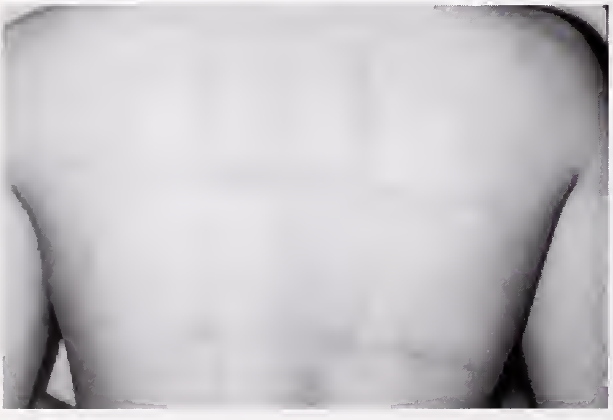

Fig. 18. Dermatographism is not uncommonly found to be cause of itching.

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Antique, Archaic and Arcane Dermatologic Instrumentation and Armamentarium

Douglas D. Altchek, M.D.

Abstract

Numerous instruments and devices have been used by dermatologists, other physicians and lay practitioners through the ages to treat skin, hair, nails, venereal diseases, and fat. And there have often been overlaps among the antique, the arcane, the bogus, and the new.

Key Words: Antique, archaic, dermatologic, history, instrumentation, instruments, quackery.

There is a very fine line between the old, the new and the arcane in considering dermatologic instrumentation and armamentarium. It is commonplace for practicing dermatologists to use instruments and devices of exceptional durability and practicality for many years. A few dermatologists have acquired or purchased practices, as well as instruments and devices, nearly a century old, from retired dermatologists. And although dermatology is a rapidly evolving field, many instruments and devices of the past are still in use today due to their fine construction and durability.

How antique dermatologic instrumentation and armamentaria came to be preserved is itself a fascinating subject. In some instances, objects (Fig. 1) were preserved by mere chance, as in the case of the volcanic eruption at Mount Vesuvius. In other instances, the objects were kept intentionally, because of their historical interest or notoriety, as in the case of the bodkins (Fig. 2). So-called "witch hunters" used these in 17th century Scotland to seek out witches. If the hapless person showed insensitivity to the bodkin, he or she was deemed a witch and could be burnt at the stake. If the witch hunter chose, he could use a "false" bodkin with a retractable needle, and condemn the innocent and the sensitive (1). Still other devices have been passed down from one generation of dermatologists to another, at times leaving no indication as to how the instrument (Fig. 3) was originally used. Finally, numerous medical museums serve as the only hope of preserving instruments and devices which otherwise would have been lost or forgotten.

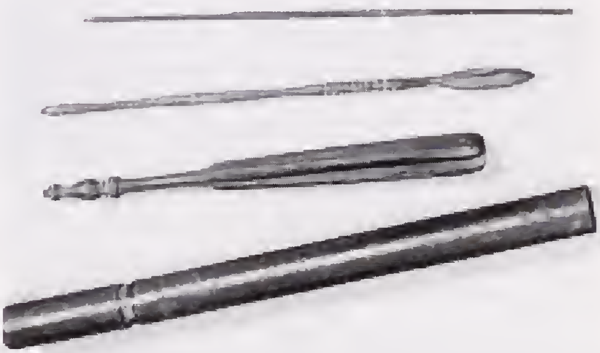

Fig. 1. Roman instruments, 1st century A.D. Courtesy of the Wellcome Center of Medical Science, London.

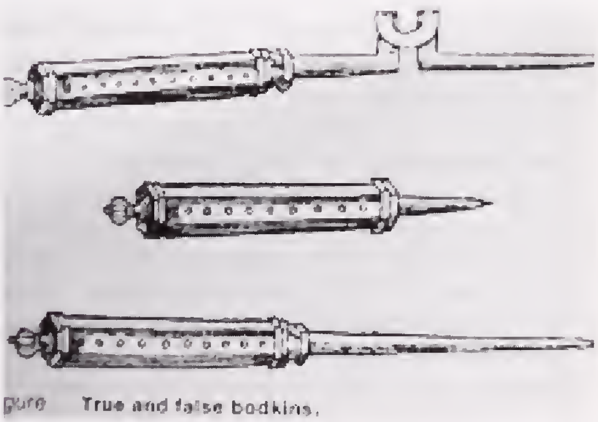
gure True and false bodkins.

Fig. 2. True and false bodkins. Courtesy of Pantheon Books, New York.

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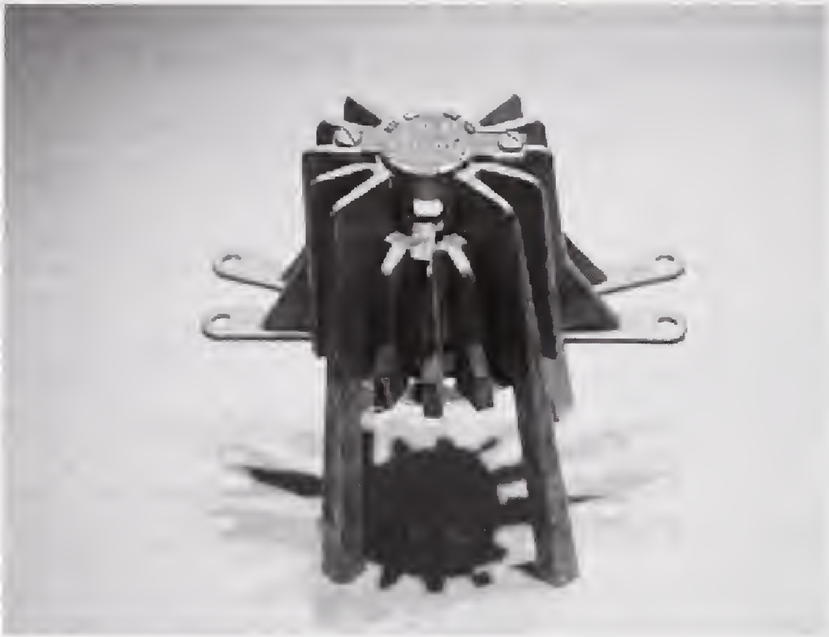

Fig. 3. Art deco device. From the collection of Douglas Altchek, M.D.

Medical antiques, especially dermatologic antiques, attract a growing number of avid collectors and enthusiasts. Dermatologic collections, however, are extremely limited, even in important medical collections in this country and abroad. New York and many other major cities do not have medical museums or even an academic interest in the history of medicine. However, collections of medical instrumentation and armamentaria in the United States include the Army Medical Museum of the Armed Forces Institute of Pathology in Washington, DC, the Dittrick Museum in Cleveland, the Bakken Museum in Minneapolis, and the Mutter Museum in Philadelphia. Great Britain's numerous medical museums are detailed in "Weir's Guide to Medical Museums in Britain" (2). The Wellcome Museum of the History of Medicine in London houses Britain's greatest collection of medical and dermatologic memorabilia. The museum's two floors of medical history are the result of the collecting zeal of Henry Wellcome, who in the early 20th century amassed a vast number of objects, which have been on display since 1982. Oddly enough, in the United States, perhaps the greatest collection of dermatologic instrumentation and armamentarium, or devices of skin and hair treatment, is housed in the Museum of Questionable Medical Devices in Minneapolis. Even though few of these devices were actually used by physicians, they have endured because of their bizarre uses by lay practitioners and of the notoriety of those who used them.

Dermatologic antique collectors have become more sophisticated and discerning. Most of their interest is now focused on the instrumentation of the pre-aseptic era, that is, pre-1890. Although dermatology was not officially established as a specialty in the United States until 1938, it had already been practiced here for nearly one hundred years. Dermatologic instrumentation made before 1890 exhibits standards of workmanship, finish, and overall artistry that were later sacrificed in the production of aseptic instrumentation (3). Earlier instruments often incorporated rare and beautiful materials in their design, including ebony, ivory, and silver, many of which would not survive the modern autoclave. Most of this artistic virtuosity had to be sacrificed for sterility. Nonetheless, some modern instruments continued to display art nouveau and art deco design, in deference to the past.

At times, dermatologic instruments come to us by sheer chance, as is the case of the bronze surgical and dermatologic instruments from the 1st century A.D., found in a block of buried objects fused together by the heat from Mount Vesuvius. Others, such as an 18th-century Persian surgical instrumentation set, were intentionally preserved, probably because of their aesthetic and artistic value (Fig. 4). The ivory handle of one scalpel is decorated with a lion's-head motif. The other scalpel is decorated with a ram's head. Precious metals and ivory adorn several of the instruments. The case or box

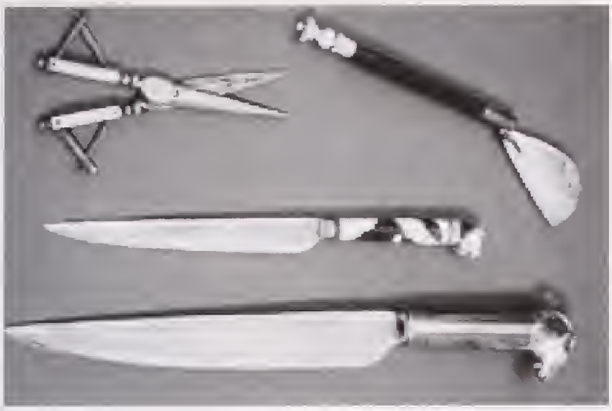

Fig. 4. 18th-century Persian instruments. Courtesy of the Wellcome Center of Medical Science, London.

containing the tools is often of great artistic and material value, for example, the container of a 17th-century European blood-letting set (Fig. 5). Bloodletting and cupping had widespread use in dermatology and other branches of medicine; it is still practiced in many parts of the world today. A 19th-century cupping set (Fig. 6) was housed in a box of sumptuous velvet. The 1871 skin testing set (Fig. 7) was contained in a mahogany case. Skin testing and patch testing continues today; however, the allergens are usually contained in plastic strips, which come packed in cardboard boxes.

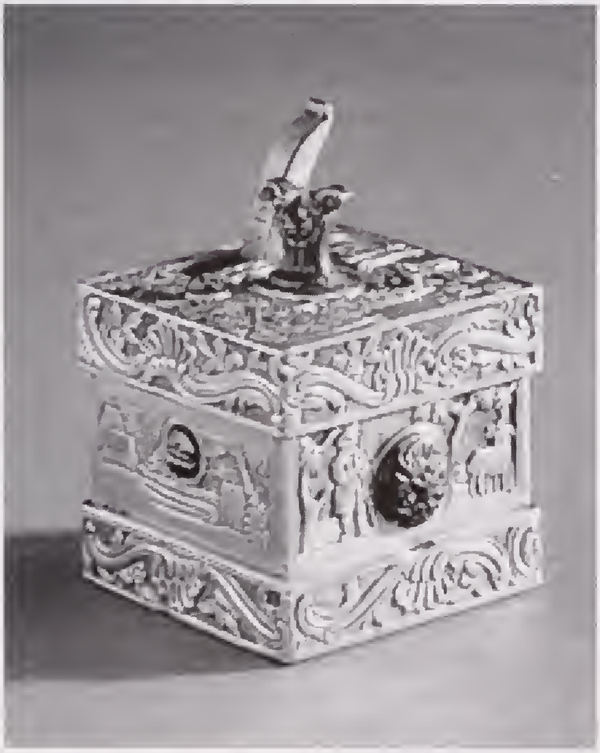

Fig. 5. 17th-century European blood-letting set. Courtesy of the Wellcome Center of Medical Science, London.

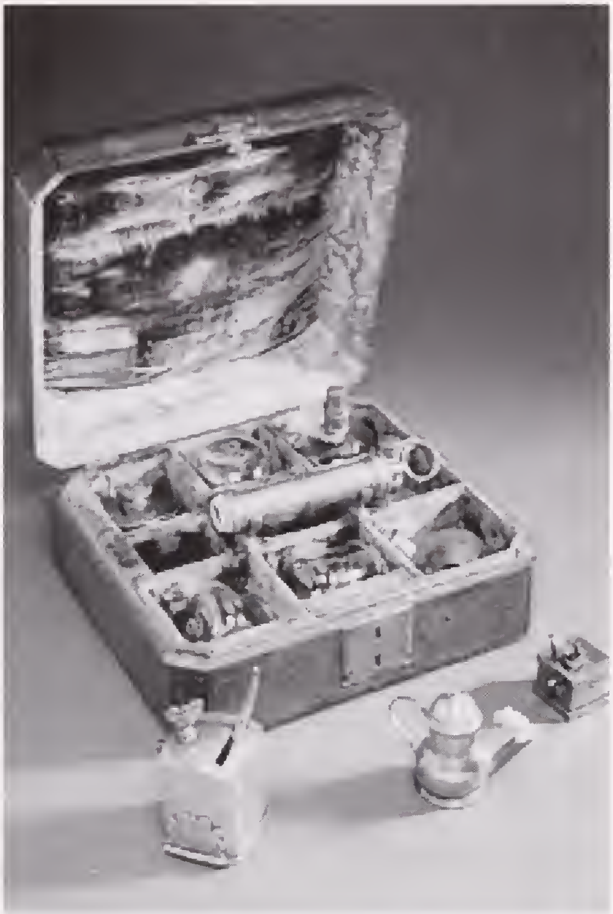

Fig. 6. 19th-century European cupping set. Courtesy of the Wellcome Center of Medical Science, London.

Dermatologic museum displays often include complete treatment suites (Fig. 8). Although the arrangement pictured was common in the 1940s, it was not uncommon to see similar ones in use until the early 1990s. X-ray therapy units and ultraviolet therapy are still the mainstays of dermatologic treatment in many offices. And many dermatologists still use X-ray therapy units that are more than fifty years old. Some X-ray paraphernalia, such as the lead shield (Fig. 9), may resemble archaeological artifacts, but they are of course still in widespread use. Some instruments, such as the Keyes cutaneous punch, although dating back to 1879, also remain in widespread use today (Fig. 10). It is the instrument of choice for performing the punch biopsy, and is the precursor of the scalp punch widely used in hair transplantation. Keyes was a professor of genitourinary surgery, syphilology, and dermatology at the Bellevue Hospital Medical College in New York City. He devised the punch in order

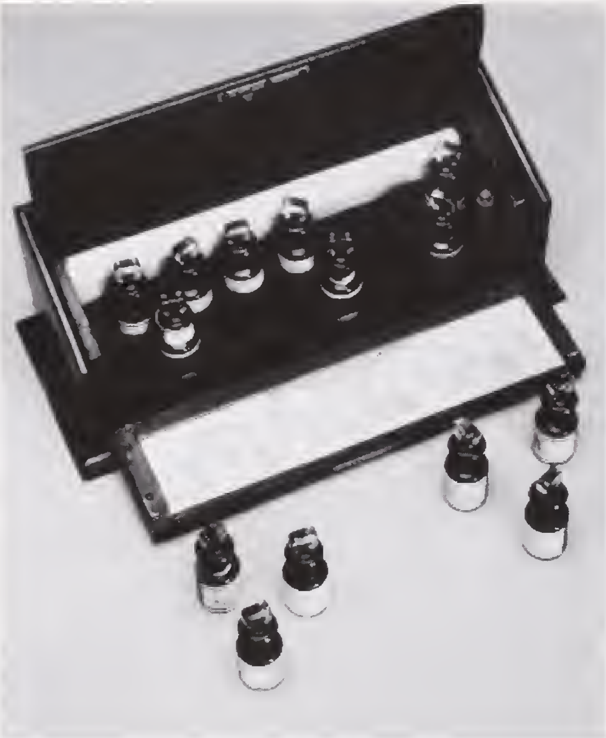

Fig. 7. Skin-testing set. English (1871). Courtesy of the Wellcome Center of Medical Science, London.

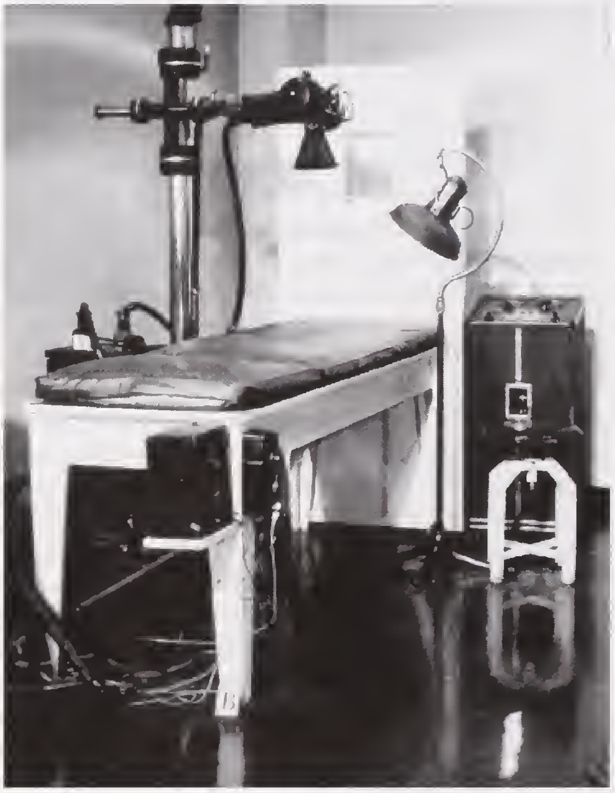

Fig. 8. A dermatologist's setup, circa 1950. Courtesy of the National Museum of Health and Medicine, AFIP, Washington, DC.

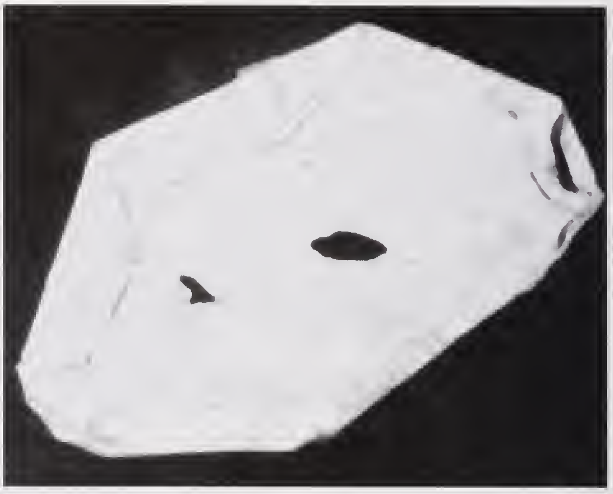

Fig. 9. X-ray therapy lead shield, circa 1980. Courtesy of the National Museum of Health and Medicine, AFIP, Washington, DC.

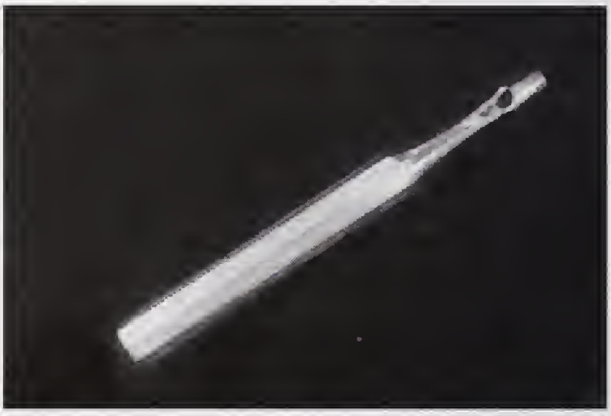

Fig. 10. The Keyes cutaneous punch, circa 1950. Courtesy of the National Museum of Health and Medicine, AFIP, Washington, DC.

to extract fireworks fragments from the face of an unfortunate patient (4).

By the turn of the last century, many instrument catalogues contained precursors of today's dermatologic instruments. Some devices used one hundred years ago later fell into disfavor and were revived recently. For example, the instrument depicted in Fig. 11, upper right, is a tattooing device for the treatment of port wine stains. Although this procedure was replaced by laser treatment, medical tattooing is again used today to create permanent eyeliner and lipliner! Other instruments of that era included the Piffard comedone extractor (Fig. 12), left center, which displays all the flowery design of the "belle epoque."

Mercury was in widespread use one hundred years ago (Fig. 13), its main dermatologic

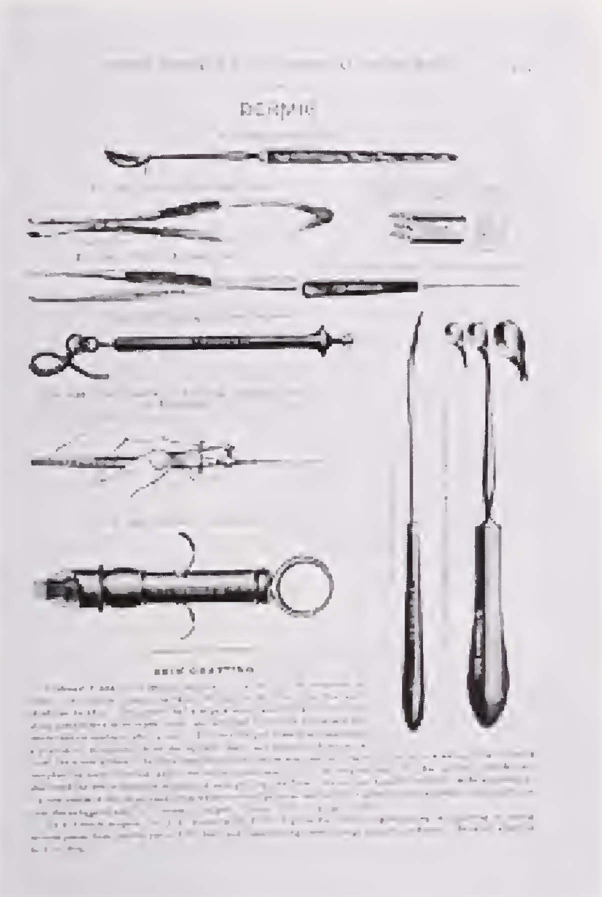

Fig. 11. Diverse instruments, including tattoo device, circa 1899. Courtesy of the Dittrick Medical History Center, Cleveland, OH.

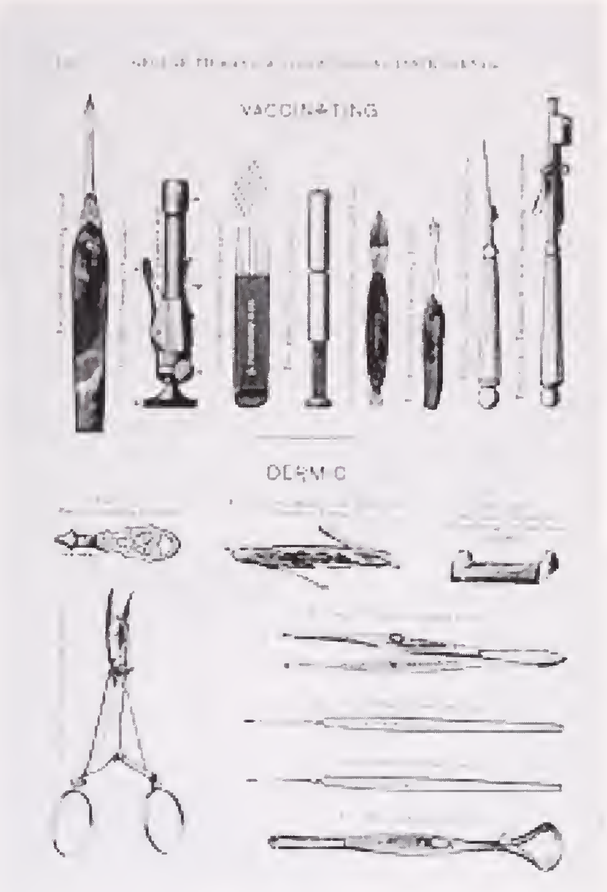

Fig. 12. Diverse instruments, including the Piffard comedone extractor (1898). Courtesy of the Dittrick Medical History Center, Cleveland, OH.

use being in the treatment of syphilis. The old adage was "One night with Venus, and the rest of your life with Mercury." Indeed, until the advent of penicillin, this was the sad reality.

In the early part of this century, ultraviolet light was a mainstay of dermatologic treatment. The dual Alpine sun lamps (Fig. 14) were considered a remarkable innovation because of the speed with which the phototherapy treatment could be accomplished. The air-cooled mercury quartz lamp (Fig. 15) was in widespread use in many physicians' offices in the 1920s. The durability of such units is testified to by the fact that, until recently, many were still in use for the treatment of psoriasis and other conditions. Numerous other devices of this era had a scientific basis, but were of little real value. The "Electrostatic Breeze" (Fig. 16) was an electrostatic generator that created a corona discharge in the air surrounding the patient. The ionization and warming effect were purported to benefit the dermatologic patient. The 1890 electric hairbrush (Fig. 17) was actually not electric but magnetic. In 1997, a hairbrush was marketed by The Sharper Image, based on a similar theory of electric stimulation.

One fascinating area of dermatologic artistry that has all but disappeared is that of the moulages, which were introduced in Europe after the Renaissance for the teaching of anatomy. With the development of medical education in the 18th century, the demand for actual teaching specimens far exceeded the available material. Wax models were an excellent means of demonstrating anatomic detail and were less perishable and odoriferous than actual specimens. When words could not easily describe certain dermatologic conditions, which were often fleeting, wax models were extremely useful. Each moulage maker, or moulager, had his own secret formula, usually consisting of paraffin, colophony, and carnauba wax (5). Production largely ceased in the 1930s, although moulages are still available in Dresden from the German Hygiene Museum. They can also be seen at numerous hospital museums

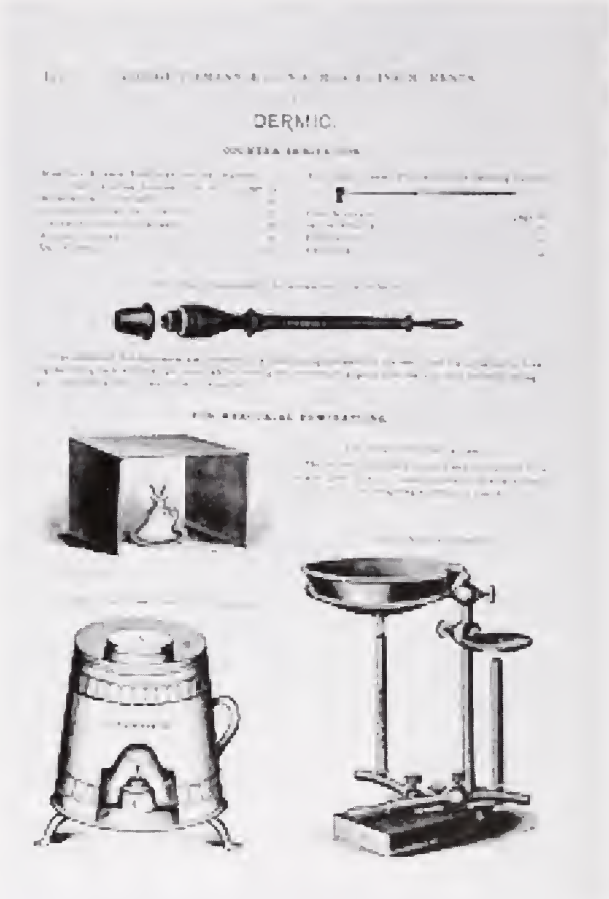

Fig. 13. Mercury fumigation unit (1898). Courtesy of the Dittrick Medical History Center, Cleveland, OH.

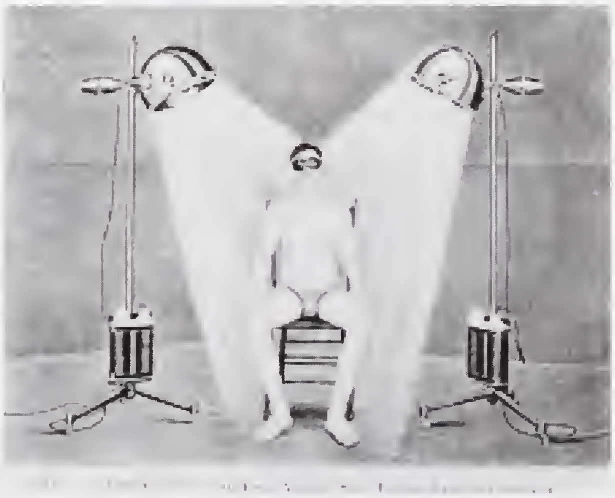

Fig. 14. The dual Alpine sun lamps (1916). Courtesy of the Dittrick Medical History Center, Cleveland, OH.

throughout the world. Two examples one of are syphilis gummosa (Fig. 18) and one of syphilis ulcero-serpiginosa (Fig. 19) (6).

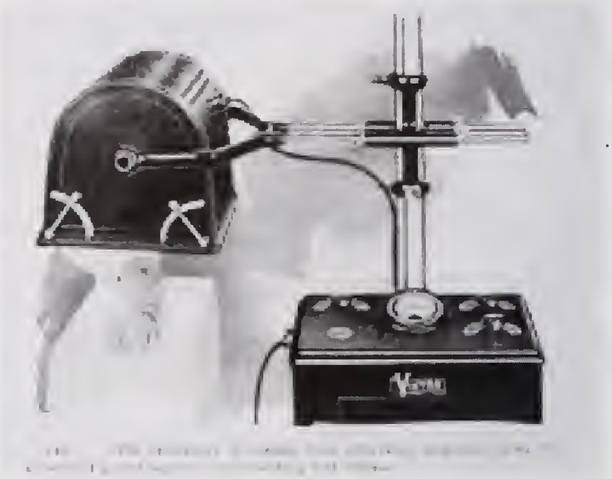

Fig. 15. The air-cooled quartz mercury lamp (1926). Courtesy of the Dittrick Medical History Center, Cleveland, OH.

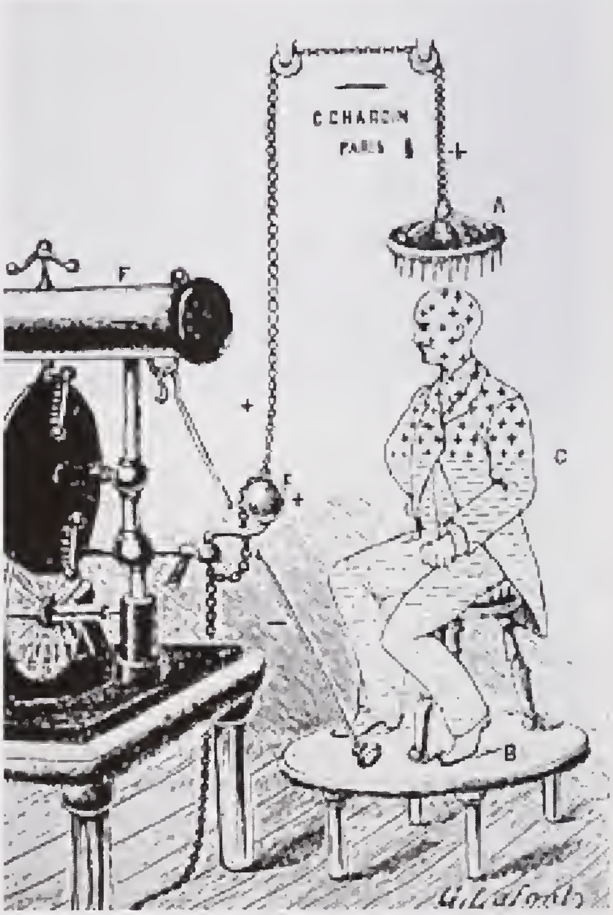

Fig. 16. The "Electrostatic Breeze" (1920). Courtesy of the Bakken Museum, Minneapolis, MN.

Until fairly recently, dermabrasion was the cosmetic surgical procedure most widely performed in this country. The Robbins dermabrader, developed by Robbins and Kurtin,

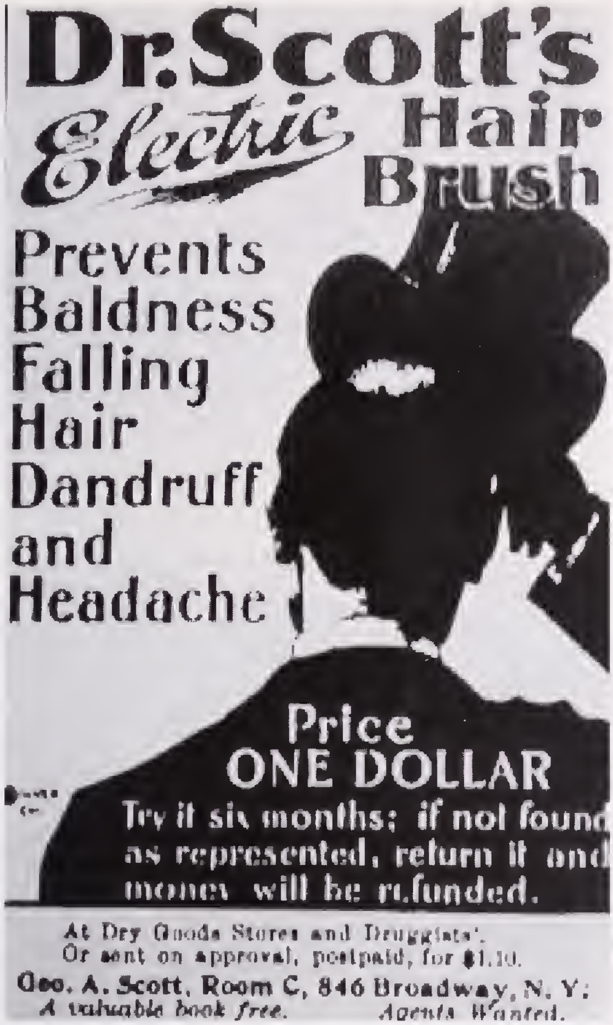

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Fig. 17. The Electric Hair Brush (1890). Courtesy of the Bakken Museum, Minneapolis, MN.

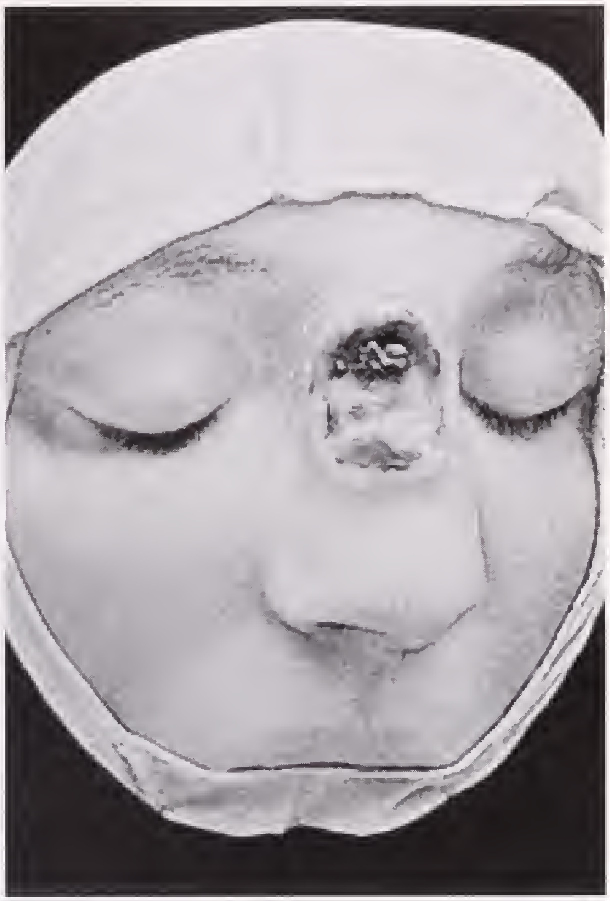

Fig. 18. Moulage of syphilis gummosa (1904).

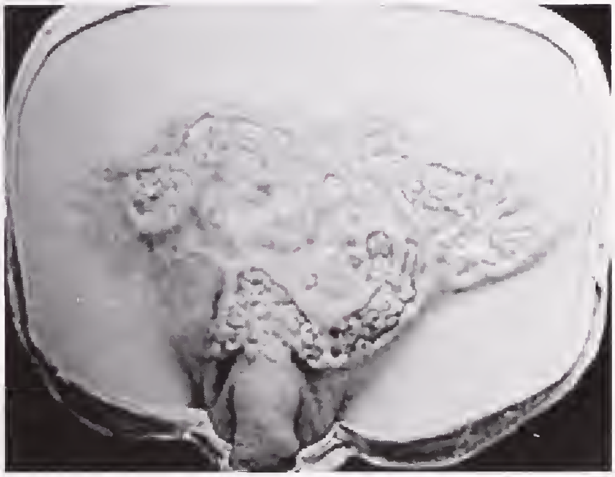

Fig. 19. Moulage of syphilis ulcero-serpiginosa (1904).

was in widespread use in offices until the early 1980s (Fig. 20). A complete dermabrasion setup in the 1960s (Fig. 21) (7) consisted of the dermabrader, electric fan, blower and the obligatory rubber raincoats worn by the operators. Since the advent of chemical peels, laser resurfacing, and more effective acne treatments, few dermatologists still perform the procedure. However, dermabrasion is still the treatment of choice for certain dermatologic conditions, such as acne scarring and disseminated superficial actinic keratoses.

The past and present in dermatologic instrumentation and armamentarium continue to coexist. On a recent visit to several dermatology offices in New York City, I noted some fine examples of older devices that are still being used. X-ray therapy is still the treatment of choice for certain basal cell carcinomas; several fine units were found (Fig. 22). Some offices prominently displayed dermatologic antiques as part of the office decoration. An "Ultraviolet Ray" which contained numerous attachments, including a hair wand for stimulating scalp growth, was found, in excellent condition, in one office (Fig. 23); many dermatologists' offices at one

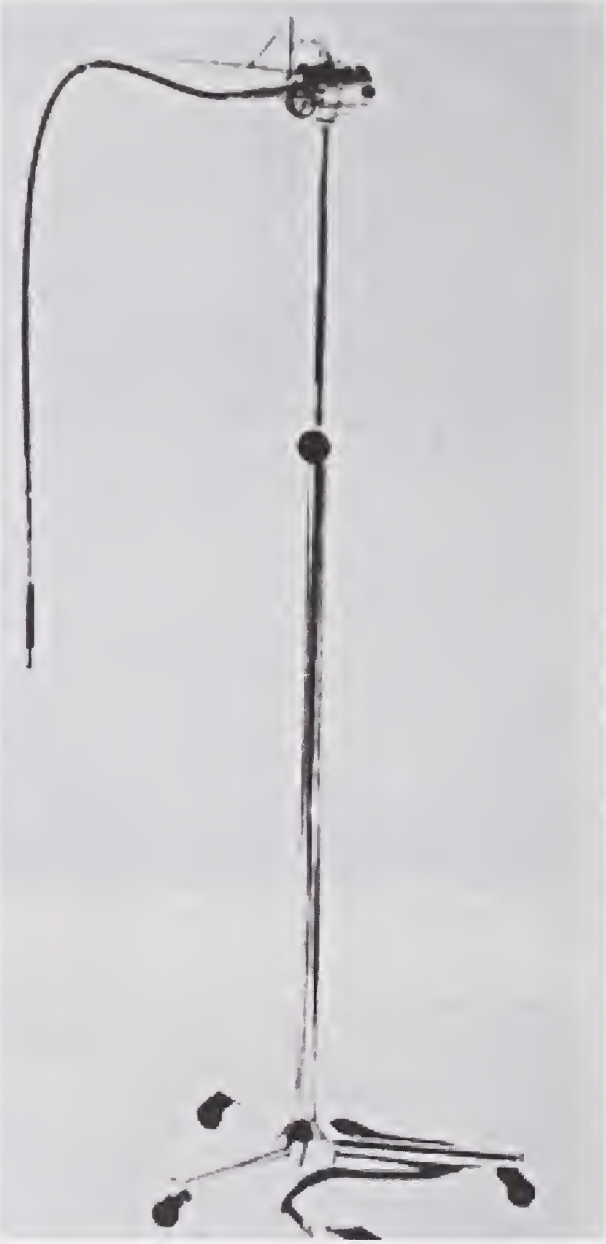

Fig. 20. The Robbins dermabrader (1965).

time employed this unit actively. An early cryosurgery unit complete with instruction manual (Fig. 24) and stereoscope, for the stereoscopic viewing of skin lesions, was found (Fig. 25). When what appeared to be an old lunch pail was opened, a hand-made tattoo gun for treating port-wine stains was revealed (Fig. 26).

A survey of another dermatologist's office revealed other items once used for therapy. On display were such items as Phillip's Contact Radiotherapy cones (Fig. 27). The Kidde dry ice apparatus (Fig. 28) produced a dry ice pencil from compressed CO_2, to treat lentigines and keratoses; working units are still being used today by several dermatologists. A variety of electrodesiccators were also on display, several of which have occasionally been brought back into service. One endothermy unit (Fig. 29) has

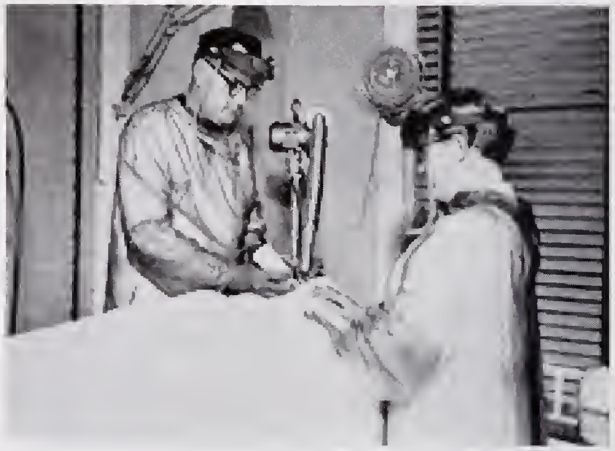

Fig. 21. Dermabrasion setup (1965) from Dermabrasion and chemical peeling, Charles C. Thomas, publisher.

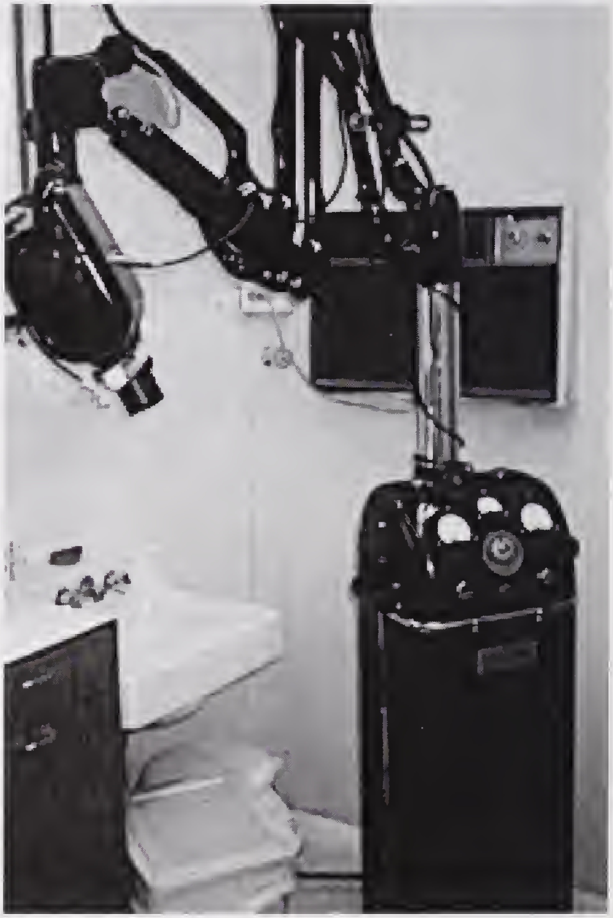

Fig. 22. X-ray therapy unit, circa 1975. From the collection of Hillard Pearlstein, M.D., New York.

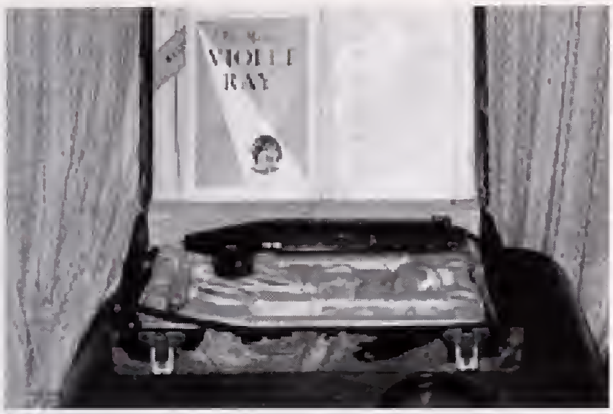

Fig. 23. The Ultraviolet Ray. From the collection of Vincent Cipollaro, M.D., New York.

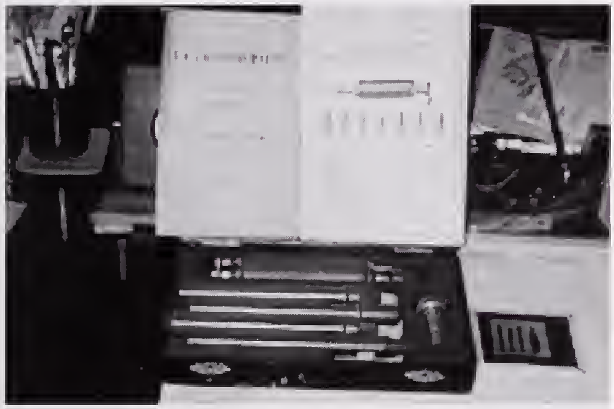

Fig. 24. Cryotherapy unit, circa 1900. From the collection of Vincent Cipollaro, M.D., New York.

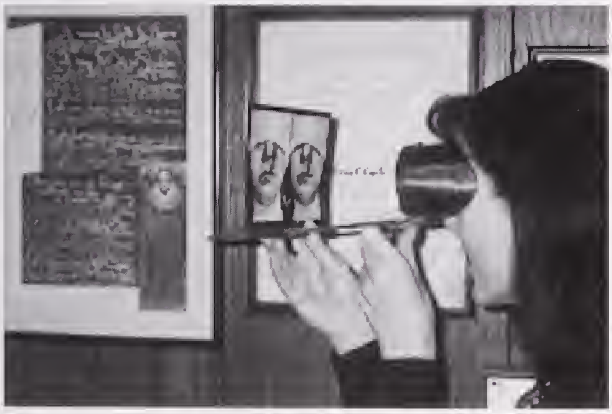

Fig. 25. The stereoscope (1910). From the collection of Vincent Cipollaro, M.D., New York.

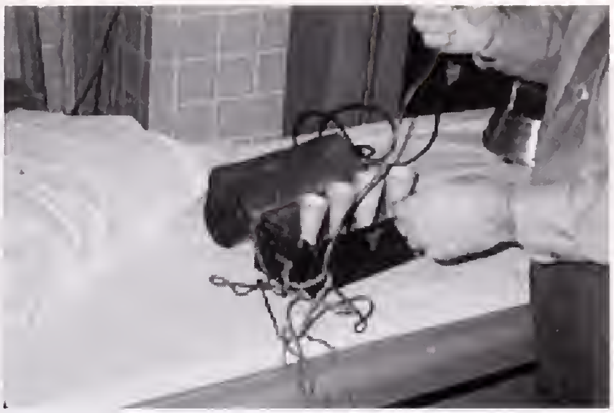

Fig. 26. Tattoo gun (1930). From the collection of Vincent Cipollaro, M.D., New York.

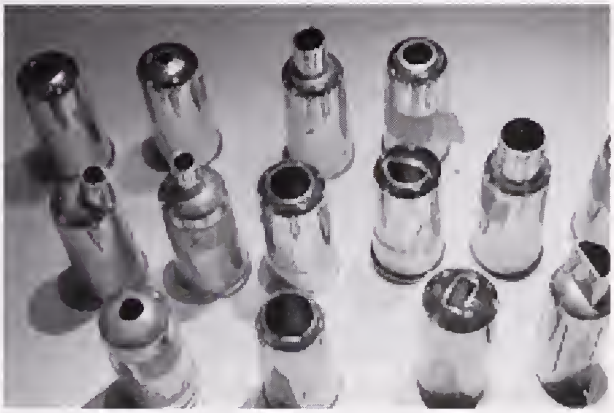

Fig. 27. Phillip's Contact Radiotherapy cones, circa 1940. From the collection of Douglas Altchek, M.D., New York.

been used to treat more than 100,000 skin cancers, while another (Fig. 30) a fine example of art deco design, is now used to decorate a consultation room. A bag of gauze-wrapped CO_2 slush, called Zeroderm, has been used at one office, since the 1930s, for the treatment of acne vulgaris and actinic keratoses because of large patient demand (Fig. 31). An art nouveau comedone expressor and an art deco curette were framed and honored as a wall decoration (Fig. 32), and a poster from 1933 expounding the benefits of yeast was on display (Fig. 33). Since the 1930s, yeast has alternately been portrayed as both a cure and cause of disease.

Outside of dermatologists' offices, perhaps no greater collection of antique, archaic, and arcane devices exists than the exhibit at the Museum of Questionable Medical Devices in Minneapolis. Although no dermatologist or physician ever used most of these devices, they are of historical and cultural interest. The Nemectron (1959) (Fig. 34) was supposedly effective in toning the body, rejuvenating the skin and restoring the cutaneous elasticity. It was also claimed to overcome acne and remove deposits of fat. Radithor (Fig. 35), a radioactive beverage popular in the late 1920s and early 1930s,

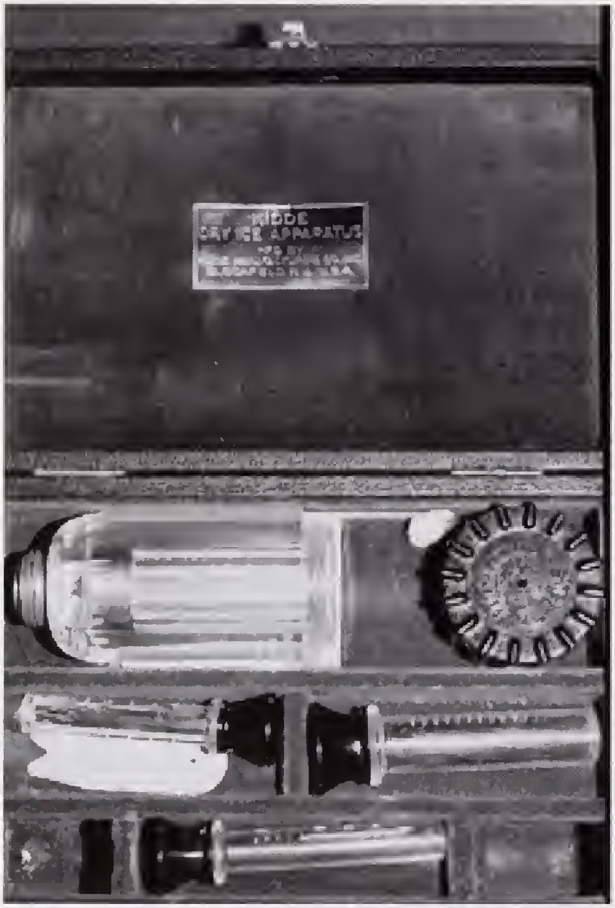

Fig. 28. The Kidde dry ice device, circa 1945. From the collection of Douglas Altchek, M.D., New York.

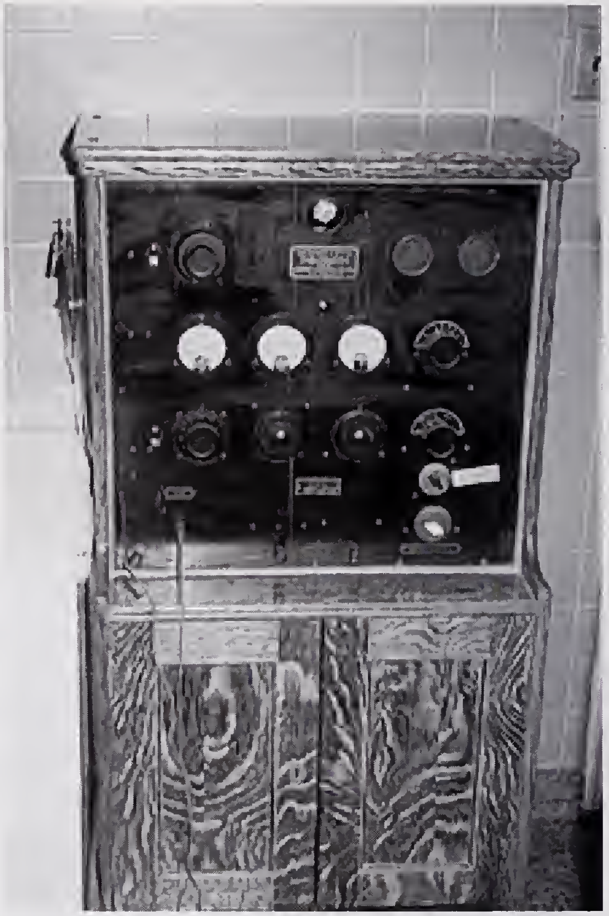

Fig. 29. The Wyeth endotherapy unit, circa 1929. From the collection of Douglas Altchek, M.D., New York.

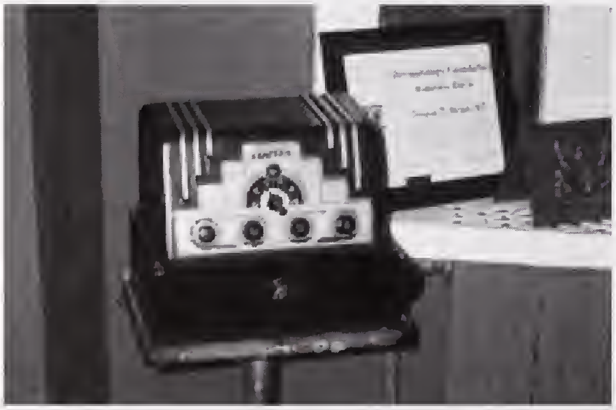

Fig. 30. The Cameron electrodesiccator, circa 1935. From the collection of Douglas Altchek, M.D., New York.

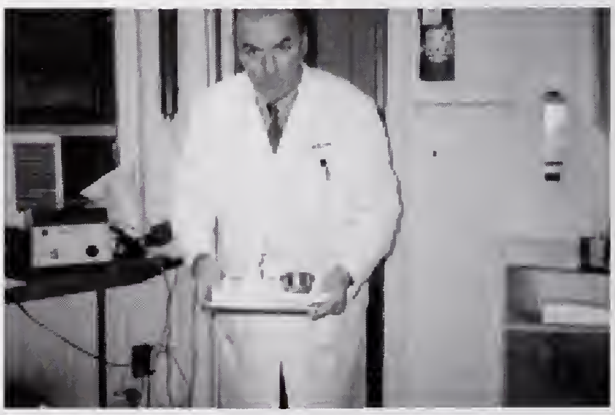

Fig. 31. Zeroderm (dry ice slush bag).

was a supposed rejuvenating tonic popularized by a steel mogul and socialite who guzzled about 1400 half-ounce bottles to improve his appearance and sexual prowess. He died of radium poisoning after losing his teeth and lower jaw. The Crosley Xervac (1946) (Fig. 36) was a device that promised to develop a deep network of blood vessels in the scalp, to promote hair growth, by applying alternating vacuum and positive pressure. The Blud-Rub (1940) (Fig. 37) was used throughout the United States for several years in barbershops to stimulate hair growth. Its real fame came when it

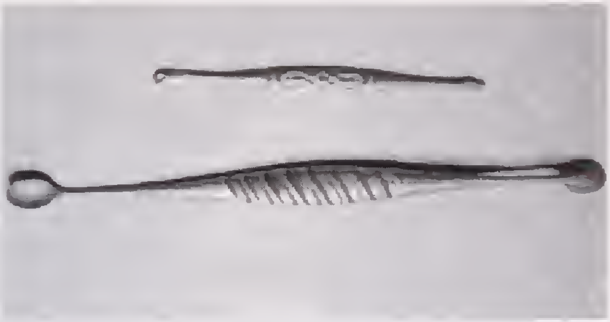

Fig. 32. An art-nouveau comedone expressor and an art-deco curette. From the collection of Douglas Altchek, M.D., New York.

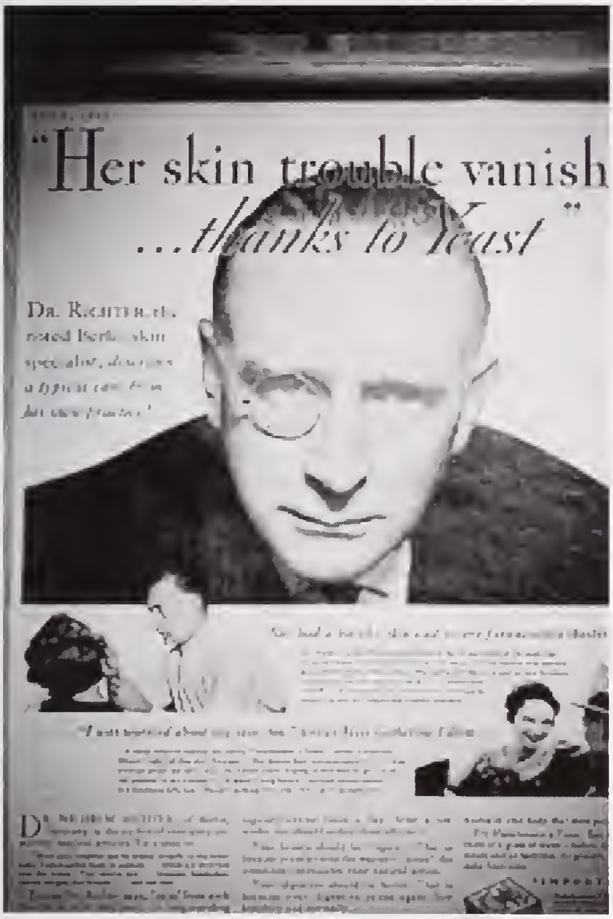
"Her skin trouble vanish
...thanks to Yeast"

Fig. 33. A Fleischmann's Yeast ad from 1933.

was used as a prop in an often-repeated "I Love Lucy" television segment, in which Lucy tried to make Ricky's hair grow by using the device and a little molasses. These, along with numerous other devices on display in the museum, are potent testimony to the distortion and perversion of science and to the gullibility of the public when presented with pseudo-scientific contraptions.

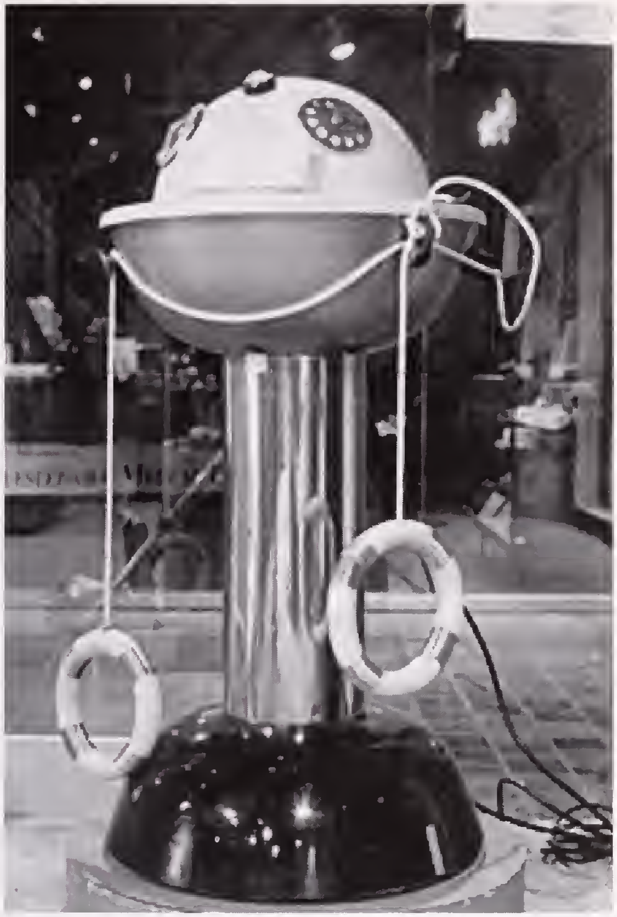

Fig. 34. The Nemectron (1959). Courtesy of the Museum of Questionable Medical Devices, Minneapolis, MN.

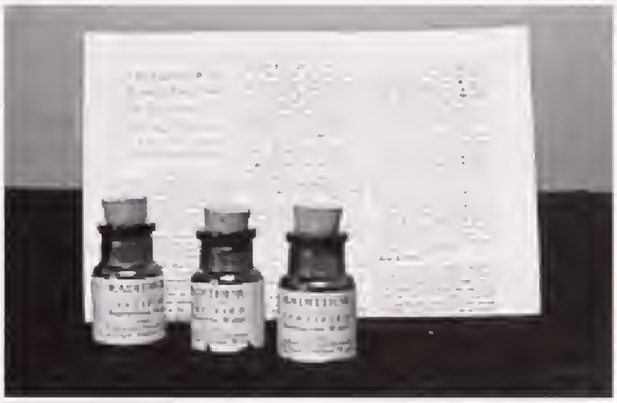

Fig. 35. Radithor (1932). From the Museum of Questionable Medical Devices, Minneapolis, MN.

Summary

There is a wealth of historical dermatologic instrumentation and armamentarium available. Although many objects may be found in museum collections, the greatest collections can probably be found displayed in dermatologists'

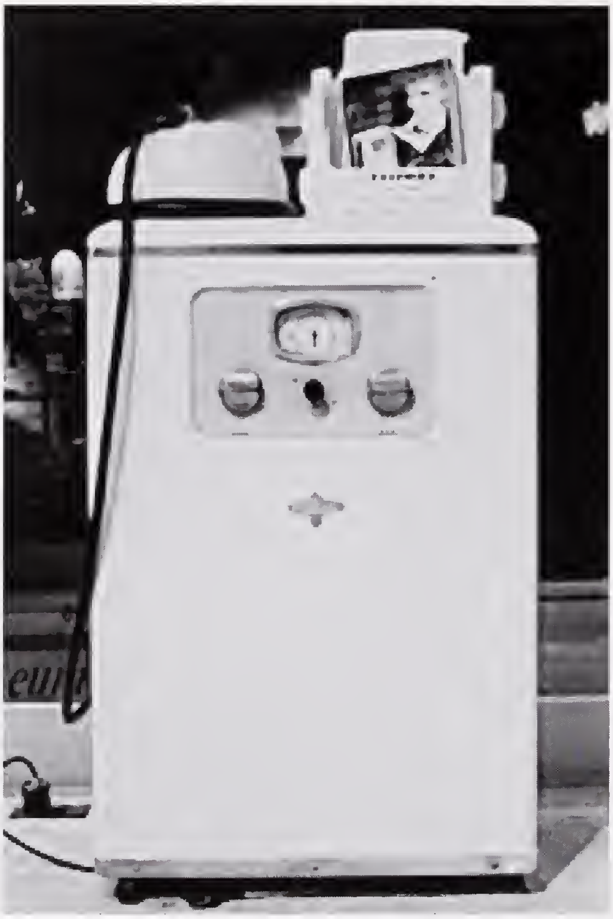

Fig. 36. The Crosley Xervac (1946). From the Museum of Questionable Medical Devices, Minneapolis, MN.

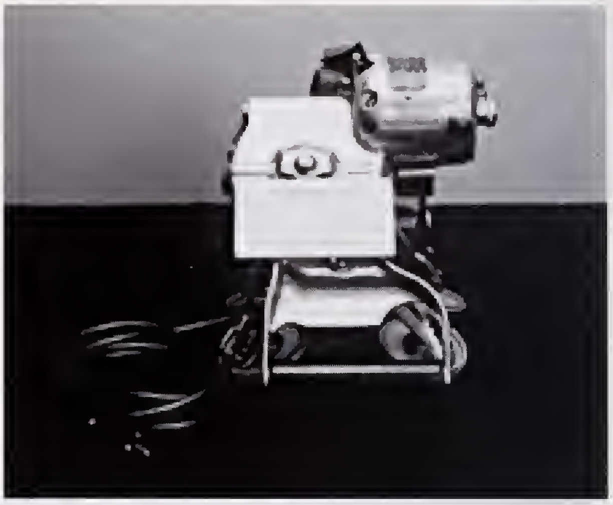

Fig. 37. The Blud-Rub (1940). Courtesy of the Museum of Questionable Medical Devices, Minneapolis, MN.

offices. Those practitioners who have shown the foresight to maintain and display objects of great historical interest and style have made great strides in preserving the rich legacy of dermatologic history. It is to be hoped that many of these artifacts will eventually be donated to medical museums so that they can be seen by everyone interested in the history of science and popular culture.

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Unilateral, Circumscribed, Chronic Dermatitis of the Papillary-Areolar Complex:

Case Report and Review of the Literature

NELSON LEE NOVICK, M.D.

Abstract

Lichen simplex chronicus is a well-described, common pruritic disorder resulting from repeated rubbing and scratching. Typically, only one site is involved. When this site involves the papillary-areolar complex of one breast, the condition is termed unilateral, circumscribed, chronic dermatitis of the papillary-areolar complex. A patient with this uncommon condition is herein reported, and the literature, including a discussion of the differential diagnosis, is reviewed. An aggressive approach to the work-up of such a patient is recommended, to ensure accurate diagnosis and initiation of appropriate therapy

Key Words: Lichen simplex chronicus, unilateral, chronic dermatitis of the papillary-areolar complex.

Introduction

CIRCUMSCRIBED, CHRONIC DERMATITIS or lichen simplex chronicus (LSC) is a well-described, common pruritic disorder resulting from repeated rubbing and scratching — a process often referred to as the scratch-itch-scratch-lichenification cycle (1, 2). Typically, only one site is involved, which may be any area that is accessible to rubbing. Sites most often affected include the ankles, as well as the pretibial and occipital/posterior nuchal regions (particularly in women). The anterior neck, hands, and anogenital areas are also frequent locations. Unilateral involvement of the nipple and the areola by LSC, however, is a relatively uncommon event, whose importance lies largely in its striking clinical resemblance to unilateral papillary and areolar lesions of other, more serious conditions, including erosive adenomatosis of the nipple and Paget's disease.

Accordingly, clinicians should remain alert to the possibility of these other entities whenever evaluating unilateral eczematoid lesions of the nipple and areola, especially in those cases that do not respond rapidly to appropriate measures directed at treating chronic eczema.

Case Presentation

An otherwise healthy 24-year-old nulliparous white female university student presented with a 3-year history of pruritus, tenderness, thickening, scaling, fissuring, drainage and swelling of the papilla and areolar region of the right breast.

The patient consulted a dermatologist at the time of initial presentation and was diagnosed as having "eczema," based upon the clinical picture and a negative direct immunofluorescence smear to rule out herpes simplex viral infection. She was immediately treated with desonide lotion 0.5% and a short course of oral lincomycin, and was later switched to fluocinolone acetonide ointment 0.025% as needed. Treatment resulted in diminished tenderness and cessation of oozing, but otherwise the patient reported only minimal overall improvement. The breast lesion persisted for more than two years, despite the above treatment. A biopsy was finally taken; it exhibited subacute spongiotic dermatitis with edema and eosinophils. The findings were felt to be most compatible with contact dermatitis. No additional work-up was performed, and the patient was advised to continue the use of her topical medications, reduce the frequency of cleansing of the affected breast, and restrict herself to mild, hypo-allergenic cleansers designated for sensitive skin. Compliance with these recommendations resulted in little change.

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Address correspondence to Nelson Lee Novick, M.D., 328 East 75th Street, New York, NY 10021.

The patient denied the use of any cosmetics, fragrances, or moisturizers on the involved region, either preceding or subsequent to the onset of the eruption. She routinely wore an unpadded bra and was not a jogger. Medication history included allergies to penicillin and erythromycin, the regular use of doxylamine succinate for sleep, and the occasional use of OTC brands of ibuprofen, naproxen sodium, or acetaminophen for periodic migraine headaches and menstrual cramping. There was no personal or family history of either atopy or psoriasis. The patient admitted to being a highly anxious person since childhood.

On examination, she was found to have an approximately 5 cm × 6 cm confluent, indurated, erythematous, dry, scaly plaque involving the right nipple and areola with gradual extension onto the skin of the right breast laterally and interiorly. Additionally, postinflammatory hyperpigmentary changes were noted at the right lower and outer regions of the areola. The nipple was not retracted. There was no evidence of fissuring or drainage from the lesion or the nipple, and no fluid could be expressed from the latter. Examination of the remainder of the breast revealed no evidence of masses or tenderness, and there was no significant lymphadenopathy. A complete skin examination uncovered no other relevant cutaneous, scalp or nail pathology.

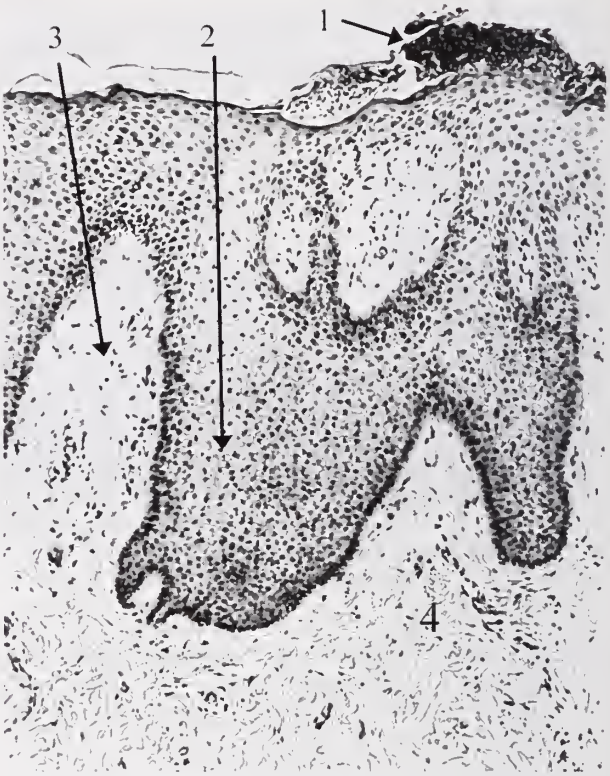

Figure. There are epidermal hyperkeratosis, acanthosis, elongation of the rete ridges, and elongation and broadening of the dermal papillae. The dermis shows a chronic inflammatory infiltrate in the upper and midlevels of the dermis and fibrosis (hematoxylin and eosin stain, X100). 1. Hyperkeratosis. 2. Acanthosis (note the elongation of the rete). 3. Elongation and broadening of papilla. 4. Inflammatory infiltrate and fibrosis in the dermis.

Three 3 mm punch biopsy specimens were taken from clinically distinct locations in proximity to the lower pole of the areola. Each exhibited histologically (to slightly varying degrees) psoriasiform spongiotic dermatitis with eosinophils, most consistent with a diagnosis of LSC, possibly of contact vs nummular dermatitis origin (Figure). A patch test screening series for contact allergens was negative at 48, 72 and 96 hours. Potassium hydroxide microscopy, fungal cultures and Wood's ultraviolet light examination were likewise negative. A bacterial swab of the region, taken for completeness, yielded no evidence of bacterial colonization or infection.

Although the underlying etiology could not be determined, the history, clinical picture and pathologic findings were most consistent with a diagnosis of circumscribed, chronic dermatitis (lichen simplex chronicus). The possibility of a prior contact dermatitis due to an antigen not contained in the patch test screening series could not be ruled out. Halobetasol propionate 0.05% ointment, a superpotent topical steroid, was prescribed for twice daily application to the entire affected area, and 0.2 cc total of triamcinolone acetonide 2 mg/cc suspension was injected intralesionally to the two most indurated and tender regions of the areola. (The injectable preparation was made by mixing 1 cc of triamcinolone acetonide 10 mg/cc suspension with 4 cc of a 10:1 mixture of lidocaine 1% and sodium bicarbonate 1 mEq/mL solutions.) Other measures included: the discontinuation of all soaps and cleansers; the use of plain, tepid water for cleansing; and substitution of regular laundry detergents and fabric softeners which are dye-free and fragrance-free for cleaning her bras and blouses. Consultation with a breast surgeon was also recommended. However, by the time of her appointment approximately three weeks later, the lesion was dramatically improved and active disease had largely been replaced by postinflammatory hyperpigmentation.

As a result, no further work-up or change in treatment plan was suggested. Two small, persistently indurated plaques on the lateral and superolateral areola required two additional treatments with intralesional triamcinolone 2 mg/cc suspension at monthly intervals before finally resolving. Following this, the patient was switched to a schedule of three consecutive applications of halobetasol propionate ointment 0.05% on weekends only (the so-called topical, intermittent, high-dose pulse therapy protocol). Six months following the initiation of therapy, the papillary-areolar lesion was completely healed without scarring or pigmentary abnormalities. There were no recurrences in a subsequent two-year follow-up.

Discussion

Viewed overall, circumscribed chronic dermatitis has been estimated to be one of the most frequently occurring skin conditions among persons aged 1–74 in the United States, with prevalence rates approaching 1 in every 250 people (3). On the other hand, unilateral, chronic, circumscribed dermatitis of the nipple and areola appears to be relatively uncommon. When it does involve this location, eczema of the nipple and areola is most often a bilateral condition. In those cases in which it is the sole presenting manifestation (i.e., when unaccompanied by eczema elsewhere on the cutaneous surface), it is typically bilaterally symmetrical in clinical appearance and extent (4).

The underlying pruritogenic stimulus in many cases of LSC often remains undetermined. Frequently, patients have a personal or family history of atopic disorders (5). In some cases, underlying contact dermatitis or frictional irritation may be the precipitating event. Whatever the trigger, psychogenic factors have long been believed to play an important contributory role in the development or perpetuation of lesions (2). Pruritus, the dominant and commonly the sole symptom, may be spasmodic, paroxysmal or continuous; it is often reported to be worse at night.

The papillary-areolar complex is composed of well-differentiated dermal papillae containing sweat glands, specialized sebaceous glands, accessory mammary glands and smooth muscle attached to the dermis. For convenience, the differential diagnosis of disorders affecting the nipple and areola can be divided into two broad categories, subdermal lesions and cutaneous lesions. Paget's disease of the breast and erosive papillomatosis are perhaps the two most important subdermal unilateral conditions of the papillary-areolar complex that must be differentiated from unilateral, circumscribed, chronic dermatitis. The differential diagnosis also includes contact dermatitis, seborrheic dermatitis, hyperkeratosis of the nipple and areola, frictional conditions, artefactual disease, and less commonly fungal infections such as tinea versicolor, tinea corporis and *Candida* of the nipple.

Paget's disease of the breast, a malignant condition, starts in the ducts below the skin of the nipple (6). Early Paget's disease is quite superficial in appearance and commonly presents as a unilateral, pruritic, "eczematoid" lesion involving the nipple and/or areola. Unlike true eczema, the edge of the lesion is irregular and tends to be well defined. If mistaken for simple "eczema" and left untreated, the nipple lesion typically becomes red, roughened and eroded. Once nipple epithelium is destroyed centrally from the ductal orifice, a crusty exudate and ultimately a palpable tumor result. Since Paget's disease accounts for 2% of all breast cancers, both invasive and intraductal, prompt diagnosis, by a simple punch biopsy or a small wedge excision, is essential. Excisional surgery is curative when performed early.

Erosive adenomatosis of the nipple is a rare, idiopathic, benign condition, which may present as scaling, erythema, induration, and later as ulceration, discharge and crusting (7). Lesions are confined to the nipple, and symptoms may include pruritus, burning and pain. Patients often have symptoms many years before the condition is accurately diagnosed, with 21 months the mean duration between initial presentation and diagnosis. The histologic picture of dilated-tubular, double-layered epithelium downwardly proliferative from the epidermis is diagnostic. Local excision is curative.

Contact dermatitis of the chest and breast due to a variety of allergens, including either the foam rubber padding or nickel-containing wires of brassiere cups and perfumes applied to the region, is well-described in the literature (8). However, allergic contact dermatitis confined to the nipple and areola appears far less commonly and has been ascribed to application of sensitizing medications to sore or inflamed nipples (8). As in all cases of contact dermatitis, management consists of determining the offending allergenic material and eliminating further contact exposure to it.

Seborrheic dermatitis, a common eczematous condition, is felt to be a constitutional diathesis, the result of an inborn physiologic predisposition. Ordinary dandruff is probably the most well-known manifestation of this disease. Lesions, which are classically found in areas of high sebaceous gland concentrations, appear as oily, scaly, mildly erythematous patches with somewhat indistinct borders. Unilateral areolar involvement has been described (9). Although there is as yet no cure, treatment with mild topical corticosteroids characteristically results in prompt temporary resolution. Recurrences are common.

Hyperkeratosis of the nipple and areola is a rare, benign condition of unknown etiology (10). Typically, it presents as a thickening and hyperpigmentation involving the entire papillary-areolar complex, resembling acanthosis nigricans or an epidermal nevus. When confined to the breast, lesions are more commonly bilateral and unassociated with other cutaneous pathology. Unilateral nipple and areolar involvement, however, is typically associated with the presence of epidermal nevi or ichthyosis elsewhere. Biopsy is important for excluding other possible etiologies. Topical corticosteroid therapy is the treatment of choice.

Mechanical factors are also occasionally responsible for nipple and areolar problems. Jogger's nipple is a well-recognized entity (11). This condition is presumably the result of frictional irritation of an unprotected warm and moist nipple against improperly fitting clothing. Chronic irritation can ultimately give rise to a picture that may mimic an "eczematoid disorder." Although the patient's history is often revealing, a biopsy to rule out other possible etiologies should be considered in evaluating equivocal cases.

Dermatitis artefacta has been an occasional cause of nipple and areolar disease (12). Establishing the diagnosis is often difficult and time consuming, although the self-induced nature of the disease may be suspected. Patients with this problem usually have undergone many investigations and even surgery before the true nature of their underlying disease becomes apparent. They are often young to middle aged, typically pleasant and cooperative and somewhat immature, although not overtly psychologically disturbed. The affect of such individuals is often found to be inappropriate to the apparent severity of their condition. Occasionally, such patients will actively seek mastectomy, and this should alert the clinician to the possibility of artefactual disease. Characteristically, the problem is chronic and recurrent; it may result in long-term disability or scarring. The condition is difficult to manage, is unfortunately not particularly amenable to psychotherapy, and is best dealt with by strong reassurance and the gradual withdrawal of medical attention. Surgery should of course be avoided.

For completeness, two infectious conditions may be included in the differential diagnosis. Tinea corporis ("ringworm"), a pruritic dermatophytic infection usually caused by *Trichophyton rubrum*, may present as a solitary, erythematous, scaly patch anywhere on the cutaneous surface, including the nipple and areola. A potassium hydroxide wet-mount preparation used to look for the presence of spores and hyphae and a fungal culture examination can be helpful in confirming or ruling out this diagnosis. In uncomplicated cases, the use of antifungal agents, such as terbinafine, usually results in prompt relief of symptoms and cure.

Pityriasis rosea may present as an isolated, annular erythematous, scaly "herald" patch anyplace on the skin, including the nipple and areola, as much as several days before appearing diffusely over the body. Finally, tinea versicolor, another fungal infection (caused by the yeast organism *Pityrosporum ovale*), may also present as an isolated, annular scaly patch on the nipple and areola (13). Wood's light ultraviolet examination, eliciting its characteristic blue-green fluorescence, and a potassium hydroxide wet mount preparation demonstrating the typical "meatballs and spaghetti" appearance of the hyphae and spores, are helpful in establishing this diagnosis. Topical anti-yeast medications, such as ketoconazole cream, are effective in eradicating most localized causes of this problem.

Since the clinical appearance of unilateral, circumscribed, chronic dermatitis of the nipple and areola may resemble destructive benign and malignant conditions, the clinician needs to maintain a high index of suspicion in dealing with presumed eczema confined to this region. A prompt and thorough work-up, including biopsy confirmation in all cases, is the safest course to follow to ensure accurate diagnosis and to prevent unnecessary delays in the recognition and treatment of more serious unilateral nipple and areolar disorders.

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Cutaneous Granulomas Masquerading as Tuberculoid Leprosy in a Patient with Congenital Combined Immunodeficiency

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Abstract

Combined immunodeficiency disorders are characterized by abnormalities in cellular and humoral immunity. This classification includes common variable immunodeficiency (CVI), a primary immunodeficiency disorder characterized by hypogammaglobulinemia, recurrent bacterial infections, and significant T-cell abnormalities. Associated autoimmune diseases include rheumatoid arthritis, pernicious anemia, idiopathic thrombocytopenic purpura, and systemic lupus erythematous. Granulomatous lesions in lymphoid tissues, solid organs, and skin have been reported. We describe a patient with CVI who developed cutaneous granulomas with perineural invasion; to our knowledge, this is a previously undescribed feature.

Key Words: Tuberculoid leprosy, cutaneous granulomas, immunodeficiency.

Case Report

A 32-YEAR-OLD MAN who had recently arrived in the U.S. from Kuwait was diagnosed with common variable immunodeficiency (CVI) in 1988, based upon subnormal immunoglobulin levels and multiple infections. These infections included herpes zoster, viral warts, purulent knee infections, oral candidiasis, chronic diarrhea, pneumonia and iridocyclitis. In 1996, a skin biopsy specimen of a lesion on the left elbow demonstrated features of a rheumatoid nodule. He had been treated with intravenous immunoglobulin with partial success. He was then referred for evaluation of persistent skin lesions that had been present for the past eighteen months. Examination revealed numerous indurated, erythematous and pink-red macules and papules located over the extensor aspect of the forearms and legs. The distribution of the lesions also included the dorsa of the hands (Fig. 1A) and feet, with particular prominence over the metacarpophalangeal and interphalangeal joints of the hands. A plaque on the left elbow had some central scaling (Fig. 1B). There was decreased sensation to pain and light touch in the C5–C6 and L3 distribution. On abdominal examination, there was splenomegaly.

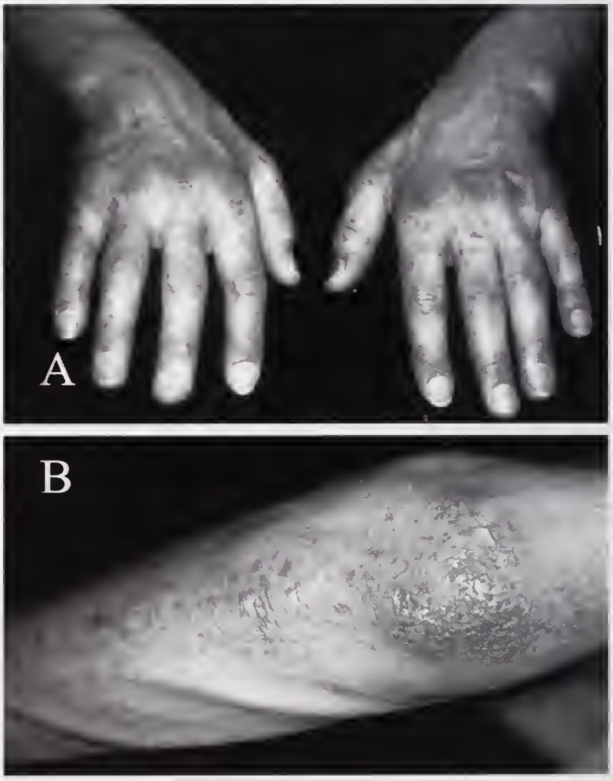

Fig. 1. **(A)** Macules and papules on the dorsa of the hands, with particular prominence over the joints. **(B)** Multiple, indurated, erythematous and pink-red macules on forearm and a plaque with superimposed scaling on the elbow.

The patient's lymphocyte screen, shown in Table 1, reveals a generalized lymphopenia with a low B-cell population.

A biopsy specimen from the left forearm revealed noncaseating granulomata in the superfi-

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TABLE 1
Patient's Laboratory Data

	Cells per mm^3	Normal range (cells per mm^3)
T total	570	750–2500
T helper	380	480–1700
T suppressor	190	200–1200
NK cells	50	135–525
B cells	10	75–375
% total B cells	1	5–15

NK = natural killer

cial and deep dermis, with prominent perivascular inflammation (Fig. 2). An unusual feature was the variable infiltration of small nerves by mononuclear cells, illustrated in the deep margin of the biopsy, which is not shown in Fig. 2. The immunohistochemistry of the mononuclear cells was positive for CD45RO, CD43, and CD68, supporting a predominantly T-cell infiltrate with occasional histiocytes. No polymorphs or eosinophils were noted. Special stains for acid-fast bacilli (including Fite and AFB) polymerase chain reaction assay revealed no evidence of mycobacterial infection. Culture for leishmaniasis was negative. Bacteria and fungi were not seen in or cultured from the biopsy specimen. A culture for echovirus was negative.

Discussion

Granulomatous lesions in lymphoid tissues, solid organs, and skin are well-recognized manifestations of chronic immunodeficiency disorders, including chronic granulomatous disease (CGD) and CVI (1). In patients with CGD, granulomas occur in the lung, liver, and gastrointestinal tract, and rarely in the skin (2). In contrast, there have been reports of cutaneous, as well as visceral and lymphoid, granulomas in patients with CVI, although the incidence rate is not known (3– 27). Fasano et al. (20) described the development of noncaseating granulomas in individuals with CVI as a "sarcoid-like" syndrome. They found 8 cases among 80 patients with CVI who had clinical findings, including multiple noncaseating granulomas, consistent with sarcoidosis (20). Two other reports tell of granulomas developing prior to the diagnosis of CVI (3, 13). Cutaneous granulomas were present in 9 of the 25 reported cases describing granulomas in association with hypogammaglobulinemia.

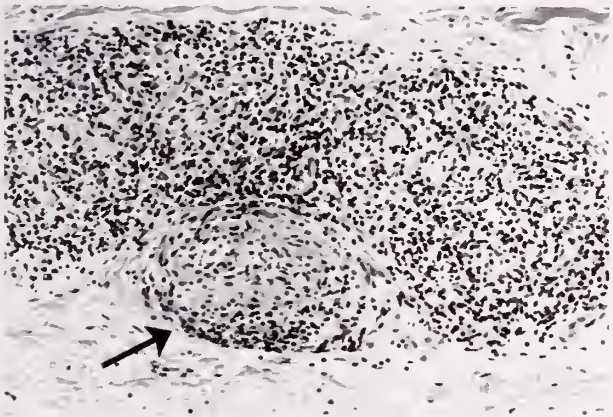

Fig. 2. Skin biopsy specimen showing mononuclear cells, primarily lymphocytes, which are focally organized into poorly formed granulomas (arrow) [hematoxylin-eosin stain; original magnification x200].

Twelve previous reports (3–11, 25–27) described 15 patients with CVI who developed cutaneous lesions (Table 2). Our patient shared many clinical features with these cases. The mean age at presentation was 33; our patient was 32. Along with indurated and erythematous lesions, there were red macules and papules. Seven of the 15 patients demonstrated scaling, which had previously received little attention (3–5, 9, 11). The most common anatomic sites were the extremities for 12 of the 15 (3–5, 8–11, 25, 26). Granulomatous skin disease in an acral pattern may be a manifestation of early immunodeficiency (3). In two reports, the lesions were noted to be prominent over the joints of the dorsal hands, similar to our case (8, 10).

The histopathologic features of this case are also similar to those seen in previously reported cases. Nine of the 15 patients demonstrated noncaseating granulomatous inflammation (3, 4, 6, 7, 9, 10, 25, 27). Three of the remaining 6 had characteristics of palisading granulomas (3, 26). This histologic picture can be associated with rheumatoid nodules, as well as with granuloma annulare and necrobiosis lipoidica (24). Interestingly, rheumatoid arthritis is a commonly encountered autoimmune disease in patients with CVI. An infectious etiology is ruled out when bacteria, acid-fast bacilli (AFB) and fungi are not found. Our patient's specimen revealed no evidence of AFB by Ziehl-Neelsen stain (3).

The skin biopsy specimen from our patient was unique in that there was perineural infiltration by granulomas. This, in conjunction with decreased sensation on physical examination, raised the possibility of tuberculoid leprosy as the underlying etiology. In our case, the biopsy showed a chronic inflammatory process that was

TABLE 2

Literature Review Summarizing Previously Reported CVI Cases with Cutaneous Granulomas.

Case	Reference	Age at Presentation (year)	Clinical Features	Location	Biopsy Results	Treatment
1	3	2	Indurated erythematous scaly papules	Face, extremities	Granulomatous dermatitis with necrobiosis	Prednisone
2	3	9	Indurated erythematous scaly plaques	Face, extremities	Granulomatous dermatitis with elastic fiber degeneration	Interleukin 2, switched to prednisone
3	3	3	Firm erythematous plaques with ulcerated crusted center	Legs, arms	Noncaseating granulomas	Prednisone
4	4	37	Scaly papules and nodules	Legs, forearm, sternum, eyelid	Epithelioid noncaseating tubercles	Prednisone
5	5	51	Scaly brown-red macules, papules, and plaques	Extremities, trunk, scalp	Nonspecific inflammatory process and caseating epithelioid granulomas	Prednisone
6	6	45	Excoriated papules	Buttocks	Nonspecific noncaseating granulomas	None
7	7	77	Macular skin rash	(not reported)	Noncaseating granulomas	Prednisolone
8	8	43	Violaceous papules	Joints of dorsal hands, elbows, knees, lumbar region	Necrotizing granulomatous inflammation	Prednisone
9	9	37	Erythematous scaling plaque and erythematous firm papules	Joints of left hand, right hand, wrist, distal arm, knees	Lymphohistiocytic perivascular infiltrate with epithelioid granulomas	Prednisone
10	10	42	Erythematous maculopapules	Legs, arms	Noncaseating epithelioid granulomas	Cyclosporine
11	10	49	Maculopapules	Legs, arms, face	Noncaseating epithelioid granulomas	Prednisolone, topical steroids
12	11	9	Indurated erythematous plaques with scaling and atrophy	Lower leg, face	Lymphohistiocytic granuloma with surrounding caseating necrosis	Prednisone
13	25	18	Reddish-violaceous firm papules	Legs	Noncaseating epithelioid granulomas	None
14	26	64	Papulonodular ulcerative rash	Right leg	Inflammatory infiltrate with central necrosis and palisading granuloma	Intravenous immunoglobulins
15	27	17	Erythematous indurated plaque	Face	Noncaseating epithelioid granulomas	None
Present Case	–	32	Indurated erythematous and pink-red macules and papules	Extremities	Noncaseating granulomas with perineural invasion	None

not highly organized, as is seen in tuberculoid leprosy and sarcoidosis. Further, AFB stains (Kinyoun and Fite) and polymerase chain reaction were negative for leprosy. Therefore, the perineural invasion may represent an extension from the prominent perivascular infiltration.

Although this patient was diagnosed with CVI in 1988 in Kuwait, x-linked agammaglobulinemia (XLA) cannot be ruled out, in view of the low number of circulating B cells. But it is unlikely that this patient has XLA, given the lack of family history, and the presence of significant T-cell abnormalities and granulomatous lesions. One patient with XLA was reported to have developed caseating granulomas (28). Patients with XLA are able to mount normal immune responses to viral infections. Our patient, however, had a past medical history significant for viral warts and herpes zoster. Patients with XLA are occasionally susceptible to enteroviral infections, such as echovirus, which affects many organs, including the skin (29). Ultimately, the distinction between CVI and XLA is made by genetic testing. The diagnosis of CVI in this patient was confirmed.

The pathogenesis of the granulomatous lesions in patients with CVI is not completely understood (3). It is hypothesized that T-cell deficiencies, antigen processing defects and an imbalance in production of cytokines are important factors in their formation (9). Others suggest a genetic mechanism supported by the frequent occurrence of a tumor necrosis factor allele in CVI patients who have had granulomatous disease (30). Granulomas in CVI may regress spontaneously or after treatment with corticosteroids. Our patient was treated with an experimental immunotherapy, interleukin-2 (IL-2), but due to his return to Kuwait, he was followed for only one month after initiation of treatment. At that time his skin lesions had not yet shown satisfactory improvement. Although the patient's histopathology resembled that of tuberculoid leprosy, an infectious etiology could not be conclusively demonstrated in his case.

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Childhood Longitudinal Melanonychia:

Case Reports and Review of the Literature

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Abstract

"Longitudinal melanonychia" refers to a brown or brown-black longitudinal band on a fingernail or toenail. A number of conditions can cause longitudinal melanonychia, but its main importance is that, in some patients, it may indicate the presence of a subungual malignant melanoma. Hyperpigmented nail bands are not uncommon in African-American, Latino and Asian patients, especially those over sixty years of age, and are often multiple in these groups. Longitudinal melanonychia is most worrisome when there is a solitary, dark, broad longitudinal band with pigment extending over the proximal nail fold (Hutchinson's sign). Such findings are considered to be a strong indication for biopsy of the nail matrix to rule out melanoma. Since nail matrix biopsy sometimes results in permanent nail deformity, and since the incidence of malignant melanoma is quite small in the pediatric age group, there is some controversy as to whether this procedure should routinely be performed in children. We report two cases of dramatic longitudinal melanonychia in toddlers and review the current literature on the management of this striking condition in the pediatric age group.

Key Words: Melanoma, children, melanonychia.

Introduction

A BROWN OR BROWN-BLACK longitudinal band on a fingernail or toenail is called longitudinal melanonychia (LM) or melanonychia striata. This condition is most commonly found in African-American, Latino, and Asian patients, especially those over sixty years of age. LM occurs more frequently on fingers than on toes, with the thumb affected in approximately one-half of all cases. Hyperpigmented longitudinal nail bands may be caused by an increase in the number and/or activity of suprabasilar melanocytes present in the distal nail matrix. They can also result from certain medications or such conditions as benign nevi or fungal infection. Whatever the cause, the results can be virtually indistinguishable upon initial presentation (1, 2). The main reason that LM is of clinical concern, however, is that it is sometimes associated with subungual malignant melanoma.

The presence of a solitary, dark, broad longitudinal band with pigment extending over the proximal nail fold (Hutchinson's sign) requires that melanoma be ruled out. Malignant melanoma is not common in children and accounts for fewer than 2% of all melanoma cases in population-based studies; however, children with malignant melanoma have a significant risk of death from the disease if diagnosis is delayed (3). Moreover, subungual malignant melanoma itself frequently has a poor prognosis due to delayed diagnosis. We reviewed the medical literature and found 83 cases of LM reported in children. We report two additional cases of LM, in both of which biopsies were done shortly after presentation. The approach to management of patients with this striking physical finding is discussed.

Case Reports

Case 1: A 2-year-old boy was seen with a pigmented area of the nail of the left index finger, which had been noticed by his parents when the boy was approximately 10 months of age. On examination there was a 2-mm-wide, centrally located linear band of pigmentation along the entire length of the nail (Fig. 1). Nail matrix biopsy revealed a lentiginous hyperplasia of melanocytes. No evidence of malignant melanoma was seen.

Case 2: A pigmented area of the nail of the right middle finger of a 2-year-old girl had been

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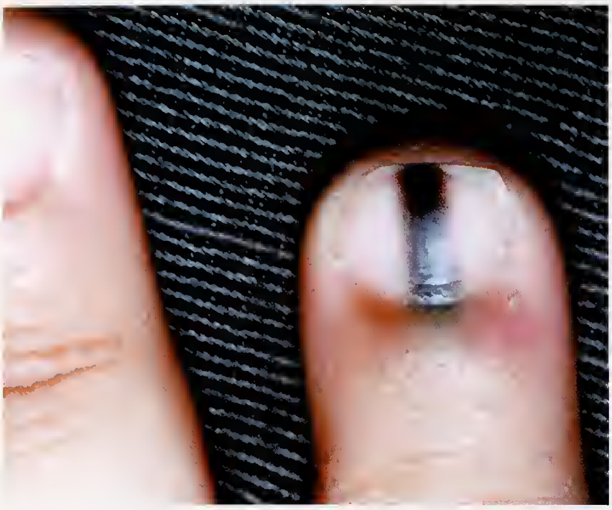

Fig 1. Two-year-old boy with a 2-mm-wide linear pigmentation of the left index finger.

noticed by her parents shortly after her birth. On examination there was a 3-mm-wide linear dark streak slightly radial to the midline along the entire length of the nail (Fig. 2). Biopsy of the nail bed revealed pigment-laden macrophages.

Operative Technique: In both cases, with general anesthesia and proximal tourniquet control for hemostasis, the nail plate was removed from the nail bed by gentle dissection with fine iris scissors. The nail fold was retracted to expose the pigmented lesion, which originated from the germinal matrix. An elliptical excision was performed. The defect was repaired under loupe magnification using interrupted fine cat-gut sutures. Antibiotic ointment was applied and the wound dressed with nonadherent gauze. In both cases, the areas healed uneventfully. One year later, no residual nail deformity was present.

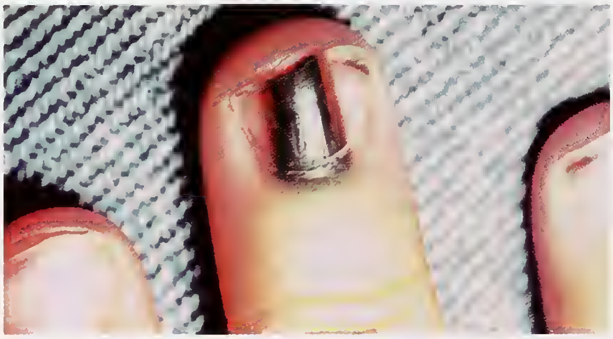

Fig 2. Two-year-old girl with a 3-mm-wide linear pigmentation of the right middle finger.

Discussion

The management of longitudinal melanonychia in children presents a formidable challenge to the diagnostician. The remote chance of discovering malignant melanoma must be weighed against the risks of general anesthesia and the potential cosmetic damage that might result from nail matrix biopsy. Diagnostic excisional nail biopsy involves significant manipulation of the nail bed and periungual area, and even in the most qualified surgical hands can result in permanent nail dystrophy. Although melanoma is overwhelmingly more common in adults, its incidence in prepubescent children is well documented (0.8 per million under age 10), prompting many dermatologists to "play it safe" and perform nail matrix biopsies, sometimes with significant cosmetic sequelae. A review of the literature on LM in children (Table) (2, 4 – 18) suggests that a more conservative approach to the management of this condition may be indicated.

The largest series of pediatric patients with LM was reported by Goettmann-Bonvallot et al. in 1999 (4). They reported on 40 patients younger than 16 years of age, seen in their nail clinic in Belgium with LM or total melanonychia. Histopathological examination revealed 19 nevi (17 junction and 2 compound), 12 lentigos, and 9 cases of functional LM defined as "melanocytic activation" in the matrix epithelium with no increase in melanocyte numbers. None of their patients had malignant melanoma. In this series, benign melanocytic hyperplasia accounted for 77.5% of LM cases overall and for 85% of cases in Caucasian patients. The remaining cases were attributed to "melanocytic activation."

Reports by Tosti et al. (5) and Labreze et al. (6) together account for 20 of the 85 total cases reported of longitudinal melanonychia in children. None of their patients exhibited malignant histology.

Several case reports involving either melanoma *in situ* or melanoma arising from a child's nail bed/matrix, are also noteworthy. Subungual melanoma, although exceedingly rare in children, has been reported on occasion. Lyall reported the case of a 12-month-old boy with malignant melanoma that arose in a congenital nevus at the tip of his right middle finger and subsequently invaded the nail bed (19). However, this case did not present as LM. Recently, Kiryu reported subungual malignant melanoma developing in a 3-year-old Japanese

TABLE

Cases of Longitudinal Melanonychia in Children Reported in the Literature

Author	Date	Ethnicity	S	Age at Diagnosis (years)	Age at Onset	Histologic Diagnosis	Notes
Buka, et al. (this paper)	2001	Latino	M	2	10 months	nevus	
			F	2	Birth	nevus	
Goettman-Bonvallot et al. (4)	1999	White (33) Black (2) Type V (5)	M=15 F=25	2 (2) 3 – 5 (6) 6 – 10 (16) 11 – 16 (16)	< 1 year (5) 1 – 5 years (13) >5 ≤10 years (9) >10 years (6) Unknown (7)	Junction nevus (17) compound nevus (2) lentigo (12) functional LM (9)	
Kiryu (8)	1998	Japanese	F	3		malignant melanoma	
Labreze et al. (6)	1996	White	M		Birth	not biopsied	No change 5 years
			M		Birth	not biopsied	No change 14 years
			M	$1^{1}/_{4}$	3 months	matrical lentigo	
			M		10 months	not biopsied	No change 5 years
			F	3	18 months	matrical nevus	
			F	4	3 years	matrical nevus	
			F	6	3 years	matrical nevus	
			F	13	12 years	matrical nevus	
Tosti et al. (5)	1996	White	M	1	8 months	compound nevus	
			F	19	Birth	compound nevus	
			M	3	12 months	junctional nevus	
			M	9	5 years	junctional nevus	
			F	6	4 years	junctional nevus	
			M	13	12 months	compound nevus	
			F	12	10 years	junctional nevus	
			M	11	7 years	junctional nevus	
			M	4	12 months	junctional nevus	
			M	5	4 years	junctional nevus	
			M	2	Birth	junctional nevus	
			M	7	4 years	junctional nevus	
Pomerance et al. (10)	1994	Japanese	F	6	12 months	compound nevus	
Ashina et al. (11)	1993	Japanese	M	11 months	1 month	nevus	
			F	4	12 months	nevus	
			M	1	6 months	nevus	
			M	10	6 years	nevus	
Kikuchi et al. (12)	1992	Japanese	F	3	Birth	not biopsied	Spontaneous resolution 13 years
			F	$1^{1}/_{4}$	1 month	not biopsied	Spontaneous resolution 6 years
			F	7	12 months	not biopsied	
			M	6	12 months	not biopsied	Fading at 9 years
Fleegler (13)	1992	Asian	M	12	9 years	nevus	
		White	F	6	24 months	junctional nevus	Atypical melanocytes

TABLE
Continued

Author	Date	Ethnicity	S	Age at Diagnosis (years)	Age at Onset	Histologic Diagnosis	Notes
			M	10	9 years	junctional nevus	Atypical melanocytes
Brantley et al. (14)	1991	White	M	1	8 months	compound nevus	
Wong et al. (15)	1991	White	M	9	Birth	compound nevus	
Kato et al. (9)	1989	Japanese	M	4	12 months	melanoma *in situ*	
			F	2	18 months	melanoma *in situ*	
			F	1	6 months	melanoma *in situ*	
Hori et al. (16)	1988		F	3		malignant melanoma	
Coskey et al. (17)	1983	White		4 months	Birth	compound nevus	
Kopf et al. (2)	1980	n/a	F	14	n/a	melan. hyperplasia	
		n/a	M	10	5 years	junctional nevus	
Ohtsuka et al. (18)	1978	Japanese	F	10 months	Birth	junctional nevus	
Leyden et al. (7)	1972	Black	F	12	Birth	nevus	

n/a = not available

girl (8). A longitudinal melanotic nail band darkened and broadened over a two-year period to involve the entire nail-bed and adjacent periungual area. Goettmann-Bonvallot agreed that this might conceivably have been a melanoma *in situ*, but raised the possibility that it might also have been a "highly-active" junctional nevus (4). These authors also consider the three melanomas diagnosed by Kato et al. to be cases of benign melanocytic hyperplasia (9). Over the last 35 years, no more than 5 of 85 children with LM (5.9%) have displayed histologic evidence of malignancy, and some of these cases have been called into question.

Confronted with a child with LM, the clinician should carefully explain to the parents the issues involved in management. The remote chance of finding a melanoma in a pediatric patient with stable LM or the small possibility of the development of melanoma later on, must be balanced against the small but real risks of general anesthesia in children and the risk of damage to the nail matrix and subsequent permanent nail deformity. Since the data suggests that the risk of melanoma is exceedingly small, some authors have suggested watchful waiting with biopsy reserved for when LM develops rapid darkening or change in width.

However, many parents will opt for matrix biopsy when presented with the survival statistics of subungual melanoma. In skilled surgical hands, this approach has little morbidity and resolves the medical problem and parental anxiety. Certainly, when periodic re-examination and/or attentiveness to change in the lesion are in doubt, it can be argued that biopsy and excision are appropriate. Ultimately, both the clinician and the parents must decide on which options to follow.

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Cutaneous Polyarteritis Nodosa after Streptococcal Necrotizing Fasciitis

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Abstract

Polyarteritis nodosa (PAN) is a necrotizing arteritis of small and medium-sized vessels. It may present with hypertension and/or renal insufficiency. Peripheral neuropathy, myopathy, joint pains, testicular pain, and ischemic myalgias may also be seen. Gastrointestinal involvement may lead to gangrene of the bowel, peritonitis, perforation, intra-abdominal hemorrhage, and pancreatitis. The cutaneous manifestations include tender subcutaneous nodules grouped along the course of superficial arteries of the lower extremities, with or without an overlying livedo reticularis. Although multisystem involvement is characteristic, sometimes only one organ or system may be involved. Associations with viral hepatitis (both B and C) and streptococcal infection have been established for PAN. Recurrent strep infections of the upper respiratory tract, streptococcal glomerulonephritis and rheumatic fever have previously been linked to PAN. This report extends the spectrum of associated streptococcal infections to include necrotizing fasciitis.

Key Words: Polyarteritis nodosa, necrotizing fasciitis.

Necrotizing fasciitis (NF) is a potentially lethal infection of the deep subcutaneous tissues that progresses to destroy fat and fascia (1). The majority of cases are polymicrobial in nature; coinfection with synergistic, facultative, aerobic and anaerobic gas-forming organisms is most common (2). When NF is caused by a single bacterial agent, group A beta hemolytic streptococcus (GAS) is the most common etiology (1). A current study reports 66% of patients with NF yielding GAS in microbiology swabs (3).

A 1997 study demonstrated that GAS-NF has been increasing in recent years (4). We describe a 35-year-old woman who developed cutaneous polyarteritis nodosa (PAN) six weeks after an episode of NF involving the same extremity. While previous studies have reported a predisposition to cutaneous PAN after streptococcal infection (5), its occurrence after GAS-NF has not been previously described.

Case Report

A 35-year-old woman was diagnosed with NF of the left lower extremity 5 years after cardiac transplantation for viral cardiomyopathy. Medications at the time of the surgery included cyclosporine, prednisone and furosemide. Multiple cultures from the left thigh identified the etiologic agent as GAS. Treatment included aggressive antibiotic therapy and emergent fasciotomy. Six weeks later, the patient presented with a painful left calf associated with myalgias and arthralgias. Examination revealed tender subcutaneous nodules with overlying erythema on the distal portion of her left calf. The differential diagnosis included erythema nodosum and cutaneous PAN. Biopsy specimen revealed vasculitis of medium-sized arteries, consistent with cutaneous PAN. The erythema and nodules cleared with intralesional triamcinolone injections.

Six months later the patient developed cellulitis of the left thigh; multiple cultures identified the agent as GAS. The cellulitis cleared with a 5-day course of intravenous clindamycin and penicillin. Eight weeks later, the patient experienced excruciating pain in her left calf while standing. The pain had increased in intensity during the past month and was extending anteriorly. Examination revealed a recurrence of tender subcutaneous nodules on the left calf with an overlying livedoid erythema (Fig. 1). The area affected measured 8 x 12 cm. Medications included daily, low-dose prednisone (5 mg). Routine laboratory studies, including complete blood count and chemistry screen, were noncontributory. Rheumatoid fac-

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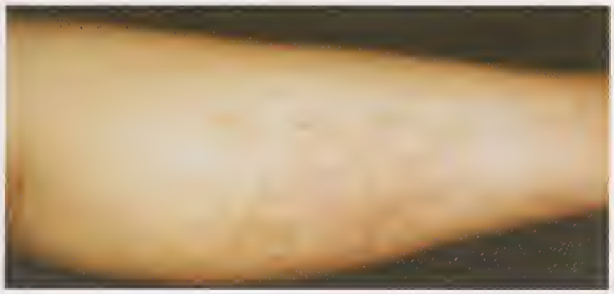

Fig. 1. Cutaneous polyarteritis nodosa. Subcutaneous nodules on the left calf with an overlying livedoid erythema.

tor, hepatitis B and C, cryoglobulins, circulating immune complexes, and ANA were negative. Repeat skin biopsy specimen demonstrated fibrinoid necrosis of medium-sized dermal vessels (Fig. 2). The patient was treated with an increased dose of prednisone (60 mg/day) and improved dramatically within 48 hours. The prednisone was tapered within a two-week period and the patient has remained symptom-free since that time.

Discussion

Many cases of NF result from an injury that disrupts the integrity of the skin: minor cuts, burns, injection-drug use, surgical procedures, insect bites and varicella infection. Blunt trauma may also increase the risk for this infection. Diabetes, arterial insufficiency, and immunocompromised states may be predisposing factors (1). Both anaerobic and aerobic organisms have been implicated. Aerobic agents include group A Streptococcus, *Staphylococcus aureus*, *Escherichia coli*, and other enterobacteriaceae (6).

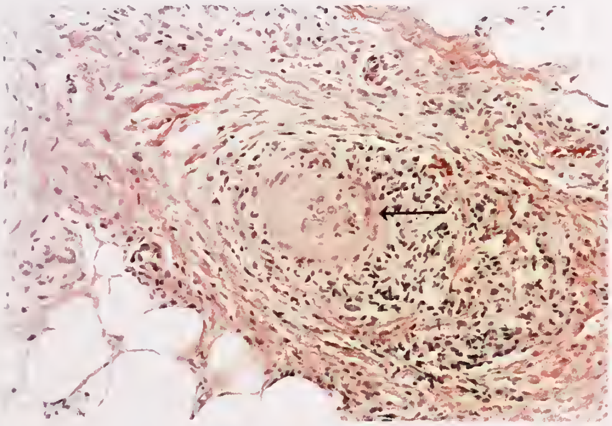

Fig. 2. Fibrinoid necrosis of medium-sized dermal vessel (arrow). (Hematoxylin-eosin stain; original magnification x 100.)

Cutaneous PAN is characterized by vascular inflammation and necrosis of small and medium-sized arteries; it has a tendency to be chronic or relapsing. Whereas the cutaneous form is limited to the skin, the systemic form of PAN additionally targets the kidneys, joints, and gastrointestinal tract (7). Renal disease and complications from hypertension account for the majority of deaths. Livedo reticularis and underlying tender, erythematous, subcutaneous nodules represent the classic presentation of cutaneous PAN (5, 7). Other cutaneous features associated with PAN include ulcers, ecchymoses, gangrene and lesions of the nailfolds and distal aspects of the digits. The lower extremities are preferentially affected (4). Arthralgias and myalgias may also be present (7).

Erythema nodosum is the most common entity with which PAN is confused. The differential diagnosis also includes other vasculitides such as Wegener's granulomatosis, hypersensitivity vasculitis, giant cell arteritis, and urticarial vasculitis (8). Diagnosis involves a high index of clinical suspicion and subsequent biopsy of the affected tissue. Laboratory testing is nonspecific and includes anemia, leukocytosis, altered renal function, urinary sediment abnormalities, and elevation in erythrocyte sedimentation rate. Rheumatoid factor, circulating immune complexes, and cryoglobulins may be present. ANCA tests are generally negative (8).

Although the pathogenesis of PAN is unknown, associations with viral hepatitis and streptococcal infection have been established (5). In 79 adult cases of cutaneous PAN, 7 patients had a history of recurrent streptococcal infection of the upper respiratory tract (5). Sheth et al. (7) describe four cases in children that were associated with previous streptococcal infection. Associations with rheumatic fever and streptococcal glomerulonephritis have also been described (7). This report extends the spectrum of streptococcal infections associated with cutaneous PAN to include NF.

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Zosteriform Darier's Disease versus Acantholytic Dyskeratotic Epidermal Nevus

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Abstract

Patients with keratotic lesions distributed in a unilateral, linear, zosteriform or localized pattern and revealing histologic features of dyskeratotic acantholysis have been reported. There is still some controversy regarding the appropriate nosologic placement of this entity. Some believe it represents a localized form of Darier's disease, while others argue it is a variant of epidermal nevus. We report a case of a 42-year-old physician who presented with a 15-year history of an asymptomatic eruption that had been diagnosed as "chronic zoster." Physical exam revealed hyperkeratotic papules and plaques in a dermatomal distribution. The controversy regarding the correct nosologic placement of such a patient is discussed.

Key Words: Zosteriform, Darier's disease, dyskeratotic acantholysis.

Case Report

The patient, a 42-year-old physician, was referred to the faculty practice for an evaluation of chronic pruritus. He was also concerned about an asymptomatic "chronic zoster rash" on the left side of his chest; it had been present for approximately 15 years. Past medical history was significant for multiple hospitalizations related to cystic fibrosis and its complications. In addition, he had been hospitalized recently for hepatic encephalopathy, renal failure and hepatic coma, and was currently awaiting both a renal and hepatic transplant.

Topical and oral acyclovir had been prescribed for the "chronic zoster rash," without improvement. There was no known relationship between the rash and sunlight exposure or hot weather. Family history was noncontributory.

Physical examination revealed multiple excoriations on the trunk and extremities. On the left side of the chest there was an obliquely oriented, band-like clustering of verrucous papules that extended from the midline to the posterior axillary line in a zosteriform distribution (Fig. 1). The papules coalesced into a linearly distributed plaque measuring approximately 28 cm x 5 cm. The remainder of the cutaneous examination, including hair, nails, and mucous membranes, was unremarkable. A biopsy specimen of a keratotic papule demonstrated thick layers of parakeratosis, broad areas of suprabasilar acantholysis, and dyskeratosis (Fig. 2). Corps ronds and corps grains were also seen (Fig. 3).

Discussion

Darier's disease is an autosomal dominant genodermatosis of abnormal keratinization recently localized to the 12q23-24.1 region on chromosome 12 (1). Onset usually occurs before 30 years of age, but may occur later. Classically, it is characterized by the presence of keratotic papules, palmar pits and a nail dystrophy. Frequently the mucosal membranes are involved. The papules are predominantly localized on the trunk and scalp, and occur symmetrically in a seborrheic distribution. The nails may be fragile and have V-shaped nicks, longitudinal red and white lines and/or ridging, and subungual hyperkeratosis. Sunlight, heat and moisture, and stress are exacerbating factors (2).

Histologic examination shows dyskeratosis with typical "corps ronds and grains," suprabasilar acanthosis, and hyperkeratosis, often with formation of papillae. The dermis may have a chronic inflammatory infiltrate in addition to some proliferation of epidermal cells (3). Further ultrastructural studies reveal

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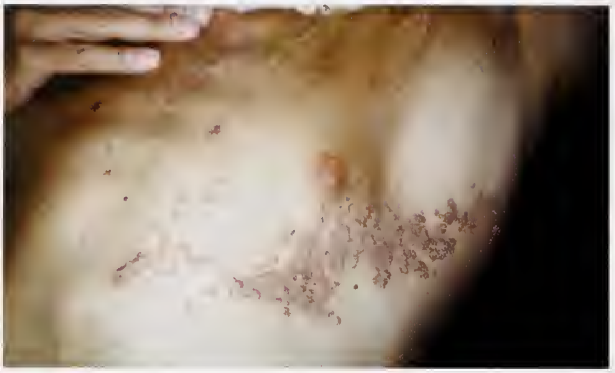

Fig. 1. On the left lower chest, there is an obliquely oriented, band-like clustering of verrucous papules that extends from the midline to the posterior axillary line in a zosteriform distribution.

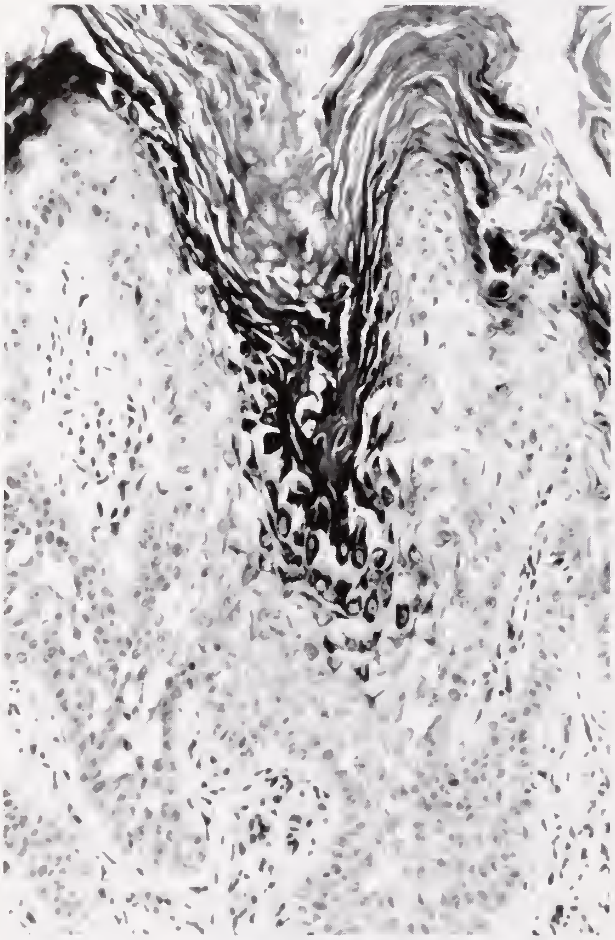

Fig. 2. Intermediate power shows suprabasilar acantholysis with dyskeratosis (hematoxylin and eosin, original magnification x 100).

breakdown of the desmosome-keratin filament complexes between keratinocytes (4).

Prior reports have noted Darier's disease occurring with other diseases. These include neuropsychiatric disorders (5), salivary gland obstruction (6), skin cancers (7), psoriasis (8), renal and testicular agenesis (9) and bone cysts (10). This is the first patient, to our knowledge, presenting with a localized form of Darier's disease in association with cystic fibrosis.

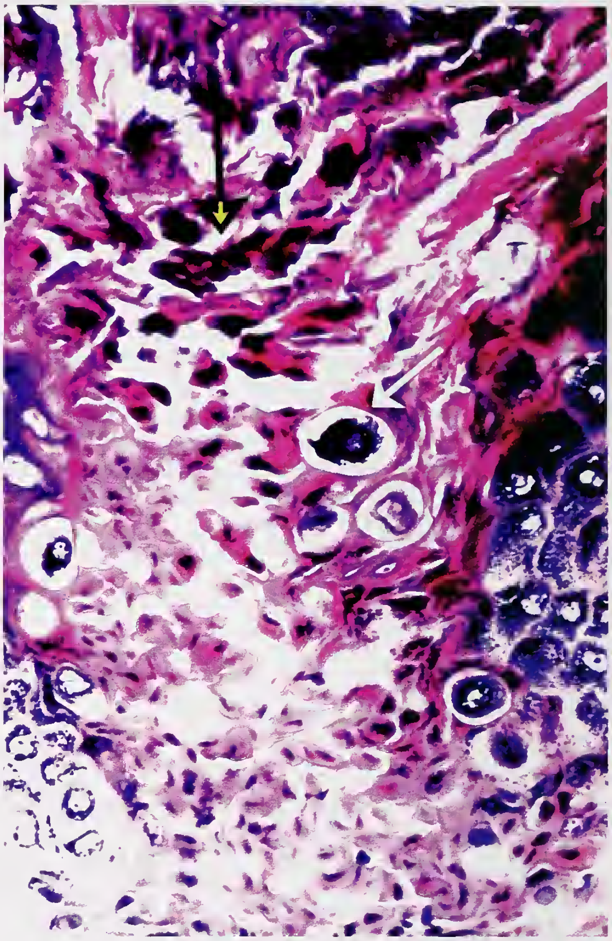

Fig. 3. Corps ronds (white arrow) and corps grains (small yellow arrow superimposed onto the black arrow) are seen (hematoxylin and eosin, original magnification x 200).

There are many reports of patients who have keratotic lesions distributed in a localized, linear, or "zosteriform" pattern that demonstrates the histopathologic features of dyskeratotic acantholysis. A nosologic controversy exists as to whether this entity is simply an unusual form of nevus or represents a variant of Darier's disease. The absence of a family history and of other associated cutaneous features of Darier's disease persuades some authors to term this entity "acantholytic dyskeratotic epidermal nevus" (11). However, there are cases of Darier's disease with typical unilateral lesions that are accompanied by other characteristic features of this disorder (12). Also reported are patients with lesions following the lines of Blaschko, with accompanying manifestations of Darier's on the ipsilateral hand (13). Some cases published as "linear" or "zosteriform" may follow these same lines, although they were not reported as such. The authors of these studies postulate a mosaic form of Darier's disease determined by somatic mutation during embryogenesis. O'Malley et al. (14) have reported four cases of localized Darier's disease and also speculate that there is a genetic basis for them. The resolution of this issue may have to await confirmation from detailed genetic analysis of additional cases.

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Announcement of 2000 Awards

The *Mount Sinai Journal of Medicine* offers several prizes for manuscripts published in *The Journal* during the previous year and judged by an awards committee to be outstanding contributions to the medical literature. The committee's task certainly was formidable, but I believe that it has chosen wisely and well. The efforts of the members are much appreciated.

The Joseph Globus Award, established in honor of the first and long-time editor of *The Journal,* is for the best overall paper on a clinical topic. The award goes to Marc N. Gourevitch, M.D., and Gerald H. Friedland, M.D., for their paper "Interactions between Methadone and Medications Used to Treat HIV Infection: A Review," volume 67 (5 & 6), pp. 429–436.

The Ralph Colp Award, in honor of the memory of a distinguished chief of surgery at The Mount Sinai Hospital, for the best paper on a surgical topic, goes to Ernest S. Mathews, M.D., and Steven J. Scrivani, D.D.S., M.D., D.M.Sc., for their paper "Percutaneous Stereotactic Radiofrequency Thermal Rhizotomy for the Treatment of Trigeminal Neuralgia," volume 67 (4), pp. 288–299.

On behalf of the Editorial Staff, I am delighted to recognize the outstanding scholarship and contributions of our year 2000 awardees to medicine in general, and to *The Mount Sinai Journal of Medicine* in particular.

Sherman Kupfer, M.D.
Professor of Medicine,
Physiology and Biophysics
Editor-in-Chief

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2. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309–315.

3. Couser WG. Glomerular diseases. In: Stein J, editor. Internal medicine. 2nd ed. Boston: Little Brown; 1987. pp. 834–861.

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Commencement Address

How Popular TV Shows Shape Public Perceptions of Medical Scientists

Harold Varmus, M.D.

Doctors, doctors-to-be, families and friends of doctors-to-be:

Thirty-five years ago, a few blocks from here, my classmates at Columbia's College of Physicians and Surgeons were joyfully receiving their diplomas. But I was finishing my fourth year elective at a mission hospital in India by hiking towards a glacier in Kashmir. With this essentially selfish act, I was missing out on some important things that you are likely to get from today's ceremony. A chance to participate in one final assembly of the people with whom you have shared a long, dramatic, life-altering experience. And a chance to allow your family and friends to look briefly at your life — to meet your classmates, to celebrate your accomplishments, and to learn about the kind of work you have chosen to do.

This last goal — to make your work understood and appreciated — is not an easy one, and it won't be fully achieved today. In fact, most of you will spend lots of time throughout your careers trying to explain your work and its demands to family and friends, patients and strangers. Given the centrality of work in our lives, I am surprised how infrequently we try to understand the labors of our fellow citizens, instead of their politics, crimes, and love lives. As someone who now thinks of himself more as a scientist than as a physician, I am often frustrated by the public's limited understanding of what it is like to be a scientist and doing a scientist's job. This is very different from the common complaint that most people don't know much about what science has accomplished. But it is equally important. In fact, a genuine understanding of science cannot be divorced from some knowledge of how scientists make discoveries, interact with their colleagues, obtain grant support, and contend with adversities.

There are, of course, exceptions to the general lack of attention to how people work. Television and movies sometimes try to show us what it is like to be an athlete, a police officer, a journalist, or a doctor. But until relatively recently, the media's perception of a physician's work has been unduly romanticized — as in the televised portrayals, popular in my youth, of Drs. Casey, Kildare, and Welby.

Several years ago that changed for the better, as I learned when my wife persuaded me to watch my first episode of "ER." It was not my last. Although at this point in its history, "ER" has come to seem a bit stale and sometimes as trivial as any soap opera, in its best moments it has been gratifyingly graphic about the intensity and physical demands of medicine as work; about the importance of collegial teamwork for delivery of care; and about the diversity of the team, with plenty of women, members of racial minorities, and even authority figures who are not doctors. Because "ER" has been a popular network show — attracting many millions of all kinds of viewers each week — those of us concerned with the public's understanding of medicine and science should be curious about what it reveals. And we who are pleased by audiences of a few hundred can only gaze in awe at an event that attracts tens of millions.

So what have the "ER" scriptwriters done with their extraordinary opportunity to educate

---

President, Memorial Sloan-Kettering Cancer Center, New York, NY.

Address correspondence to Harold Varmus, M.D., President, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

The following talk was delivered to the Mount Sinai School of Medicine, New York, NY, Class of 2001 on May 11, 2001. It has been slightly edited for publication.

Key Words: Medical scientists, public perception of medical scientists.

as well as entertain? Perhaps surprisingly, that opportunity has not been entirely lost. For example, on one pre-Christmas show, a 35-year-old man was brought to the ER unconscious after a ski-mobile accident. An imaging procedure showed a herniated cerebral hemisphere, and a signed transplant donor card was found in the patient's wallet. So Dr. Peter Benton, the impulsive surgical resident, contacted a national tissue-matching program by computer, hoping to find suitable recipients for a heart, a liver, and two kidneys. He did this despite warnings from his supervisor that a reluctant relative could overrule the signed donor card. Naturally, when the patient's estranged, guilt-ridden wife turned up, she wanted a second opinion about the verdict of impending brain-death. Time was running out. Helicopters from three cities were heading for Chicago to pick up organs. Benton was agitated. Mark Greene, "Dr. Nice Guy," bailed Benton out by talking sympathetically with the wife, who then signed a permit allowing the helicopter pilots to fly back to waiting patients with their Christmas gifts.

All in all, this episode told a remarkably realistic and ultimately moving account of current practices in the world of organ transplantation. It introduced viewers to the concept of brain death, the legalities of organ donation, the existence of computerized matching services, the urgency of transporting donated organs, and the anguish of the patients waiting for them. I would be surprised if the show did not produce greater acceptance of organ donation; certainly, it increased understanding and promoted altruism.

I have been especially interested in "ER's" portrayal of research. The most dramatic emergency medical practices pose special problems for clinical investigation. Informed consent is impossible when patients are unconscious and relatives are unavailable. During my tenure at the NIH, we and the FDA developed ways to perform studies on such patients in an ethical manner. Still, the show has been understandably reluctant to depict research efforts that might improve care of this unusual class of patients. But "ER" also weaves many other kinds of medical disorders, even chronic diseases, into its episodes. So there have been opportunities to show a wide range of medical research activities. But, disappointingly, for the first several years of its popularity, "ER" depicted research in a singularly negative and cynical fashion.

This was first made apparent to me through the portrayal of the arrogant, even satanic vascular surgeon, Carl Vucelich. Dr. Vucelich was testing a new procedure for the repair of dissecting aortic aneurysms, and his stature at the hospital depended on the research funds he brought in from a pharmaceutical company. His clinical research methods were entwined with the show's story line for several months after Peter Benton helped him repair an elderly woman's aneurysm and the patient fared poorly after the operation. Vucelich consoled Benton by attributing the outcome to her preoperative condition rather than to the procedure itself. By deeming her inappropriate for inclusion in the study, Vucelich was also increasing the fraction of patients who benefited from the procedure. Benton seemed bewildered by this *post-facto* manipulation, but did not object. As a reward, he was invited to join the research team and was provided with some pleasant perks: a parking space near the hospital, a key to a quiet room for study, and a check for accruing patients.

The medical student John Carter was then drawn into the research project. Carter, of course, is now, as you soon will be, a doctor. (Like me, he missed his commencement exercises, though he was on a mission of mercy. Dr. Benton also missed his, to do an emergency hemorrhoidectomy!) Carter was understandably tempted by the $1000 bounty Vucelich offered for finding patients with aneurysms. The temptation was so great that Carter's first claim was based on a radiological reading made by his girlfriend, after he missed the diagnosis. This patient, a relatively young man, also did poorly. So Vucelich also excluded this patient from the study. Benton then confronted Vucelich with an accusation of biased exclusion, but was too fearful of the consequences to submit a written complaint.

Up to this point, the story is interesting and even instructive about clinical trials, even if hardly flattering to medical science. In fact, it presaged by several years some of the recent aberrations in clinical trials that have now prompted a long-overdue national debate about conflicts of interest in medical research. And viewers were exposed to the classic dilemma of the whistleblower and an institution's need to respond to allegations of wrongdoing — important issues in current discussions of misconduct in science. Unfortunately, these issues were treated in a stereotyped and cynical fashion, presenting a distorted picture of how institutions handle such problems. Not too surprisingly, when Benton finally registered a written complaint, it was not taken seriously, and the episode ended with the announcement that Benton had been named Resident of the Year. His nominator? Carl Vucelich!

Clinical trials have not been the only object of "ER's" scorn for research. When an MD/PhD student turned up in the ER for a rotation, he was notably disorganized, incompetent with patients, and roundly ridiculed. Finally, when he left footprints of radioactivity on the ER floor from shoes contaminated in his laboratory, he was booted. Other efforts to incorporate research have focused on the imperative to do research for career advancement, on sloppy methods used to gather data, and on frivolous research objectives.

There is plenty here to disturb those of us who think research deserves a more balanced hearing. Of course, I don't expect a show like "ER" to risk sacrificing its entertainment appeal for the purposes of people like me. But some of the episodes I have described prove that serious issues — like transplantation or the conduct of research — can be confronted in interesting ways for a mass audience.

Some years ago, Leon Lederman, the Chicago-based Nobel Prize-winning physicist and educator, and a former colleague of Dean Rubenstein, proposed a network show called "The Dean," to portray the work and ethical dilemmas of scientists in a dramatic serial to be set in a high tech university. But he was unable to find a major sponsor. So those of us who believed that the public would welcome serious airings of such topics had to plead with the writers and producers of established shows like "ER" to tell our stories.

A couple of years ago, I had a chance to make that plea. The "ER" team was surprised by the evidence for a persistent pattern of maligning research. Some months later, when Alan Alda played a physician forced into retirement by early signs of Alzheimer's disease, I was pleased to watch his character cheered by an opportunity to enroll in a clinical trial conducted by a kindly neuroscientist.

Still, this effort did not constitute a full portrayal of what it means to be a physician-scientist in the age of the genome, that impending transformation of medicine for which we are honoring Eric Lander today. But my remaining hopes for introducing a mass audience to stimulating accounts of medical science at its best were revived last year by the unveiling of a new show whose central character was a medical scientist, played by a terrific actor, Andre Braugher. Moreover, this new show, "Gideon's Crossing," was based in part on *The New Yorker* essays by Jerome Groopman of Harvard Medical School, who is himself a serious investigator and compassionate physician.

Let's ignore for the moment the troubling article from last week's *New York Times*, which suggests that Mr. Braugher's character will have to become "more accessible to audiences" by shedding his "humorless and self-righteous" attributes and by "dating women," in order to survive the competition from comedies, conventional dramas, and old movies. Instead, I'd like to recall one of the episodes that caught my attention last fall.

Dr. Gideon was conducting a study of a new anti-leukemic drug, referred to as a "gene-blocker." One of his patients, a middle-aged man with chronic leukemia, had a long police record. After Dr. Gideon's female colleague enrolled this unorthodox patient in the clinical trial of the "gene blocker," the patient was incarcerated again and thereby disqualified from the trial. Gideon respected this rule; his colleague did not. She stole a supply of the drug from a locked cabinet and delivered it to the patient by concluding her visit to him in prison with a "meaningful" (that is, drug-full) kiss. But what interested me more than this bizarre kiss was a glance at the label on the bottles of "gene blocker." There it was, clear as day: STI-571. Verisimilitude. Few viewers were likely then to have shared my thrill of recognition. But this drug, STI-571, was described, by an act of Providence, in *The New York Times* this very morning, because the FDA has just announced rapid approval of the drug for the treatment of a common form of adult leukemia. At the time that the show aired, this drug was still in clinical trials and said to be showing phenomenal benefits. This was especially exciting to "molecular types" like me, because the drug was chosen for testing on the basis of its selective ability to inhibit the activity of a specific enzyme believed to be the cause of the leukemia. In fact, this part of the story, invisible to the television audience, seemed to me far more interesting than anything happening on the screen, where Gideon's rule-breaking colleague was in jail waiting for Gideon to bail her out.

What then is so fascinating about this new drug and the way it was discovered? Finding STI-571, with its effects on that enzyme, required the insights of many inspiring scientists over the past forty years. These include a pair of "cell gazers" in Philadelphia, who, in 1960, with relatively crude methods, noted a bizarre chromosome in leukemic cells from adults; a woman scientist in Chicago who figured out which two human chromosomes had fused to make the bizarre chromosome; teams in Holland and the U.S. who learned that a particular cancer gene was activated by that chromosomal rearrangement; American virologists who taught us what that cancer gene was and the kind of enzyme it made; pharmaceutical chemists who found and synthesized inhibitors of the enzyme; and astute clinicians who designed the drug trials. And brave leukemic patients who were rewarded almost uniformly with beneficial effects on their disease. Clinical scientists realized correctly that the drug could help a few others with rare intestinal tumors caused by changes in certain genes. Even FDA regulators and advisors exerted enormous efforts to evaluate the drug in record time.

Now, how do we turn these inspiring people and their achievements into stories that can teach the public the challenge and satisfaction of doing work like this?

As each of you now enter our profession — whether as ER resident or medical scientist — your lives will be affected by public perceptions of what you do. Consider my unorthodox digression today on popular TV shows as one manifestation of concern about how the work that you and I do is perceived. As you go proudly from this place to do a lifetime of good deeds, let us find better ways to describe that work to our friends and family, and to the society we serve.

Thank you and good luck.

Gibbs Memorial Lecture

Unifying Hypothesis of Body Fluid Volume Regulation:

Implications for Cardiac Failure and Cirrhosis

Robert W. Schrier, M.D., and Tevfik Ecder, M.D.

Abstract

Body fluid volume regulation is critically important in maintaining life. In this paper, we review our unifying hypothesis of body fluid volume regulation, which maintains arterial circulatory integrity in health and disease. The integrity of the arterial circulation, as determined by cardiac output and peripheral vascular resistance, is the predominant determinant of renal sodium and water retention. Arterial circulatory integrity can be disturbed either by a decrease in cardiac output, as in low-output cardiac failure, or by a decrease in peripheral vascular resistance, as in high-output states such as high-output cardiac failure and cirrhosis. The resulting arterial underfilling is sensed by baroreceptors that are located in the left ventricle, the aortic arch, the carotid sinus and the renal afferent arterioles. Decreased activation of these receptors during arterial underfilling leads to neurohumoral compensatory responses, which include the stimulation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system (RAAS) and the non-osmotic release of vasopressin. These compensatory responses maintain arterial circulatory integrity by increasing peripheral and renal arterial vascular resistance together with renal sodium and water retention. However, over the long term, these adaptive responses may have detrimental effects, such as pulmonary congestion, increased myocardial demand, increased cardiac afterload, ascites and hyponatremia. The intensity of the neurohumoral responses correlates with the progression and severity of both cardiac failure and cirrhosis. The understanding of the pathogenesis of sodium and water retention in cardiac failure and cirrhosis has led to therapies that favorably affect the morbidity and mortality of these patients.

Key Words: Body fluid volume regulation, arterial underfilling, cardiac failure, low-output cardiac failure, high-output cardiac failure, cirrhosis.

Introduction

Body fluid volume regulation has been a focus of research of investigators for decades. In the 19th century, the famous French physiologist Claude Bernard expressed the importance of the homeostatic mechanisms for humans when he wrote that "the constancy of the *milieu interieur* is the condition of free and independent existence" (1). In 1909, Ernest Starling emphasized the critical role of the kidney in body fluid homeostasis when he stated that "the kidney presents in the highest degree the phenomenon of 'sensibility,' the power of reacting to various stimuli in a direction which is appropriate for the survival of the organism, a power of adaptation which gives one the idea that its component parts must be endowed with intelligence" (2).

The kidney's role in sodium and water retention, both in cardiac failure and in cirrhosis, has been studied with many paradoxical results. It was initially thought that the reason for the increased sodium and water retention in these disorders was a decrease in plasma volume (3). However, after accurate measurement methods became available, plasma volume was found to be increased in both cardiac failure and cirrhosis (4, 5). Intrinsic renal mechanisms are not the primary cause of the sodium and water retention in these diseases. Specifically, it is known that successful heart and liver transplantations totally reverse the renal sodium and water retention in cardiac failure and cirrhosis (6). Moreover, a kidney transplanted from a cirrhotic patient with ascites to a recipient

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with normal liver function also functions normally without causing sodium and water retention (7).

Borst and De Vries (8) suggested that the afferent signal for renal sodium and water retention in edematous disorders was diminished cardiac output as seen in low-output cardiac failure. However, sodium and water retention can occur in conditions of increased cardiac output, such as cirrhosis, sepsis, large arteriovenous fistula and pregnancy (9–11). Thus, cardiac output alone could not explain the sodium and water retention in edematous disorders.

The efferent limb of the body fluid volume regulation was also associated with perplexing findings. It is known that a decrease in glomerular filtration rate (GFR) leads to sodium and water retention. However, renal sodium and water retention can occur in patients with cardiac failure or cirrhosis before the GFR falls (12, 13). Thus, decreased GFR is not the primary factor for sodium and water retention in these disorders.

The regulation of arginine vasopressin (AVP) is very sensitive to osmotic changes. A 1–2% change in extracellular fluid osmolality alters AVP release in a manner that maintains normal osmolality. However, patients with both advanced heart failure and cirrhosis may have severe hypo-osmolality (14). Thus, factors other than the osmotic regulation of AVP must be involved in water retention in these edematous disorders.

The renin-angiotensin-aldosterone system (RAAS) is activated in patients with advanced heart failure (15) and cirrhosis (16), suggesting that it may play a role in enhanced sodium and water retention. However, pharmacological doses of the mineralocorticoid hormone, aldosterone, cause only limited sodium retention and do not produce edema in normal subjects (17). In contrast, patients with cardiac failure or cirrhosis do not demonstrate this "escape" from the sodium-retaining effect of aldosterone, and become more edematous (15, 18, 19).

The discovery of the hormone atrial natriuretic peptide (ANP) provided another possible explanation for sodium retention in cardiac failure and cirrhosis (20). It was thought that sodium retention in these disorders could be due to a deficiency of this hormone. However, plasma ANP level was found to be increased, not decreased, in heart failure (21, 22) and cirrhosis (23–25). These are some of the perplexities that challenged biomedical scientists for many years — in their efforts to understand how body fluid volume and composition are regulated.

Unifying Hypothesis of Body Fluid Volume Regulation

It is known that plasma volume is expanded in patients with advanced cardiac failure and cirrhosis, yet the normal kidneys are retaining sodium and water (4, 5). About 85% of the plasma volume is located on the venous side of the circulation and only about 15% on the arterial side. The arterial blood volume comprises less than 2% of the total body fluid. It can therefore be hypothesized that total plasma volume, which is mostly on the venous side of the circulation, could be expanded in cardiac failure and cirrhosis, yet arterial underfilling could occur due to a decrease in cardiac output. As noted already, however, renal sodium and water retention can occur in conditions of increased cardiac output, such as pregnancy, cirrhosis and high-output cardiac failure. Based on this, a unifying hypothesis of the body fluid volume regulation has emerged (Fig. 1) (26, 27). According to this hypothesis, arterial underfilling can be caused by a decrease in either cardiac output or arterial vasodilation, as occurs with a decrease in peripheral vascular resistance. All the responses after initiation of arterial underfilling are compensatory, in order to restore arterial circulatory integrity. In low-output cardiac failure there would be a secondary increase in peripheral vascular resistance, whereas in circumstances of decreased peripheral vascular resistance there would be a secondary increase in cardiac output because of the decreased cardiac afterload. In both conditions, renal sodium and water retention would occur to maintain arterial circulatory integrity.

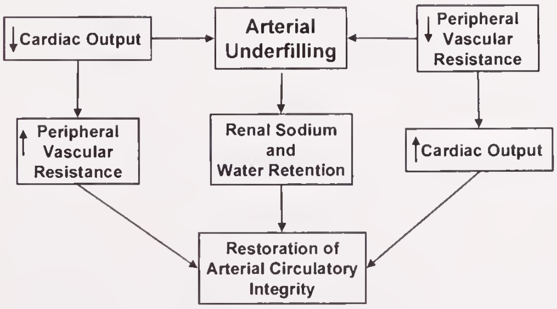
↓Cardiac Output
Arterial Underfilling
↓Peripheral Vascular Resistance
↑Peripheral Vascular Resistance
Renal Sodium and Water Retention
↑Cardiac Output
Restoration of Arterial Circulatory Integrity

Fig. 1. Body fluid volume regulation hypothesis. Reprinted with permission (27).

Low-Output Cardiac Failure

Low-output cardiac failure may lead to arterial underfilling due to a decrease in cardiac output. Other conditions of decreased cardiac output, such as volume depletion, pericardial tamponade, constrictive pericarditis, decrease in oncotic pressure due to protein-losing states and hypersensitivity reactions which increase capillary permeability and loss of colloid from capillaries, may cause arterial underfilling (Fig. 2) (26). The arterial underfilling is sensed by baroreceptors that are located in the left ventricle, the aortic arch, the carotid sinus and the renal afferent arterioles. The resulting activation of these baroreceptors stimulates the sympathetic nervous system (SNS), which activates the RAAS and causes the non-osmotic release of AVP. Increased levels of angiotensin II contribute to the impaired renal escape from the sodium-retaining action of aldosterone in cardiac failure. The non-osmotic release of AVP contributes to the water retention.

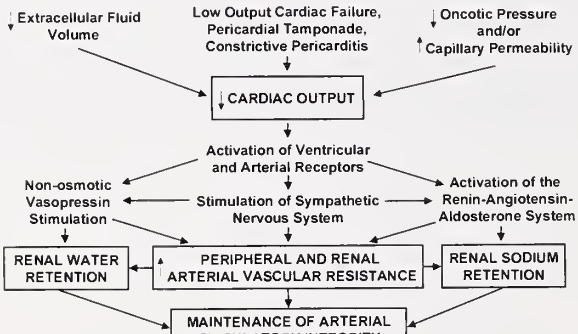
↓ Extracellular Fluid Volume
Low Output Cardiac Failure, Pericardial Tamponade, Constrictive Pericarditis
↓ Oncotic Pressure and/or ↑ Capillary Permeability
↓ CARDIAC OUTPUT
Activation of Ventricular and Arterial Receptors
Non-osmotic Vasopressin Stimulation
Stimulation of Sympathetic Nervous System
Activation of the Renin-Angiotensin-Aldosterone System
RENAL WATER RETENTION
↑ PERIPHERAL AND RENAL ARTERIAL VASCULAR RESISTANCE
RENAL SODIUM RETENTION
MAINTENANCE OF ARTERIAL CIRCULATORY INTEGRITY

Fig. 2. Sequence of events in which reduced cardiac output initiates renal sodium and water retention. Reprinted with permission (26).

In the progression of cardiac failure, as cardiac index decreases, a compensatory increase in neurohumoral response and plasma volume is observed (Fig. 3) (28). The neurohumoral response is characterized by increased plasma levels of AVP, renin, aldosterone and norepinephrine. These neurohumoral changes compensate for the arterial underfilling by causing sodium and water retention, which increases total plasma volume. Even the "normal" levels of these hormones in early cardiac failure are in fact excessively increased, considering the plasma volume expansion, which would actually suppress these hormones in a normal individual.

	CLASS II	CLASS III	CLASS IV
Cardiac index	↓	↓↓	↓↓↓
Plasma hormones (AVP, renin, aldosterone, NE)	Normal	↑	↑↑
Plasma volume	↑	↑↑	↑↑↑

Fig. 3. Neurohumoral and plasma volume responses to progressive cardiac failure. New York Heart Classifications II, III and IV. AVP = arginine vasopressin; NE n Norepinephrine. Reprinted with permission (28).

The intensity of the neurohumoral response correlates with the severity of cardiac failure. Plasma norepinephrine concentrations provide a prognostic index of survival in heart failure (29). As shown in Fig. 4, patients with heart failure who have plasma norepinephrine concentrations greater than 800 pg/mL have the worst prognosis, with a one-year survival rate of 20%. Pretreatment serum sodium concentrations in patients with heart failure correlate with plasma renin activities (Fig. 5). Moreover, serum sodium concentration is a powerful predictor of cardiovascular mortality in heart failure (30). As shown in Fig. 6, patients with a pretreatment serum sodium concentration of less than 130 mEq/L have a one-year survival rate of about 20%.

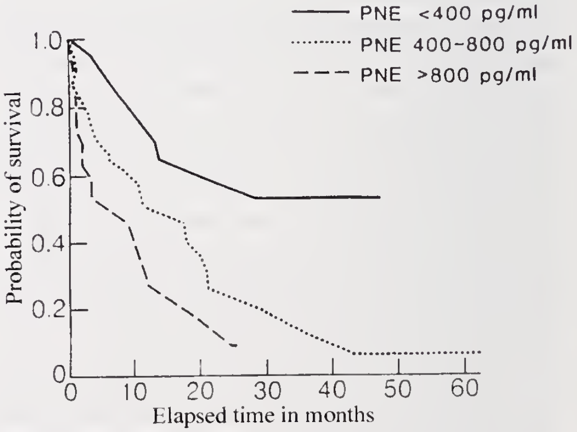

Fig. 4. Life-table analysis of survival, according to tercile, based on level of plasma norepinephrine (PNE). The probability of survival in each group was significantly different from the probabilities in the other two groups. Reprinted with permission (29).

It was previously thought that the water retention in cardiac failure must be mediated totally by intrarenal mechanisms, because the

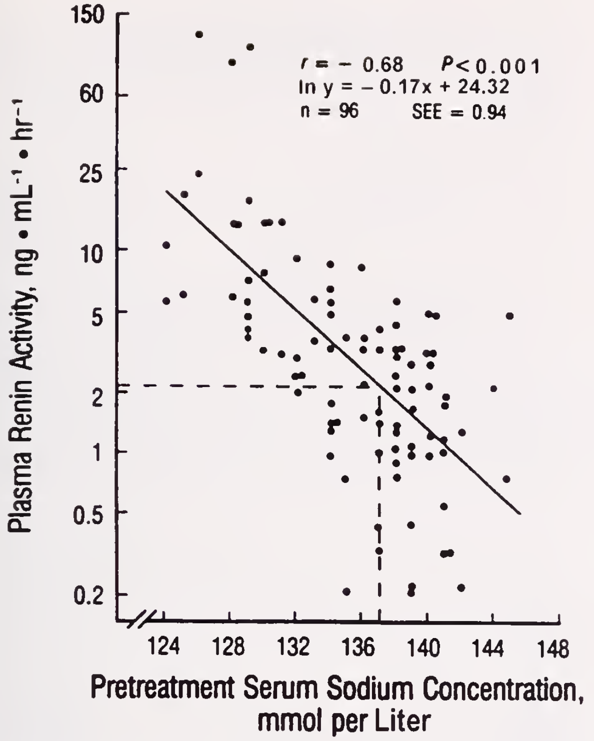

Fig. 5. Relationship between serum sodium concentration and plasma renin activity before vasodilator therapy in 96 patients with severe chronic heart failure. SEE = standard error of the estimate. Reprinted with permission (30).

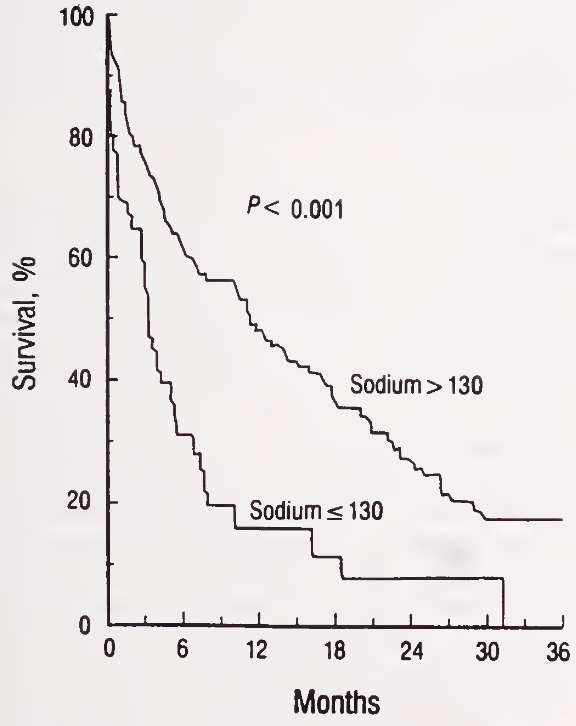

Fig. 6. Kaplan-Meier analysis showing cumulative rates of survival in patients with heart failure stratified into two groups based on pretreatment serum sodium concentration (>130 vs. ≤130 mEq/L). Reprinted with permission (30).

bioassay method could not consistently detect increased AVP levels in cardiac failure patients who were hyponatremic. However, this bioassay method was insensitive and could only detect plasma AVP concentrations above 10 pg/mL. After the development of a sensitive radioimmunoassay, it was shown that normal urine concentration and dilution occur in response to plasma AVP levels between 0.5 and 4 pg/mL, values that were not detectable with the bioassay. Szatalowicz et al. (31), by using a sensitive radioimmunoassay technique to measure AVP, showed that plasma AVP levels were not suppressed, despite the presence of hyponatremia in patients with congestive heart failure (Fig. 7). This study was the first to demonstrate the non-osmotic release of AVP in hyponatremic heart failure patients. Kim et al. (32) extended this observation by showing that messenger RNA (mRNA) for AVP was significantly

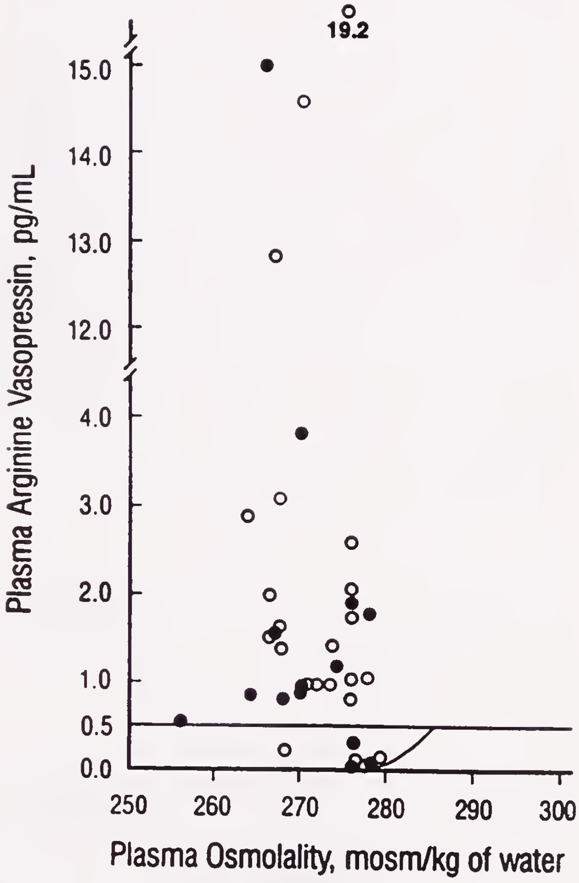

Fig. 7. Plasma arginine vasopressin (AVP) in 37 hyponatremic patients with congestive heart failure. Patients who never received diuretics before measurement of AVP are represented by solid circles, and those who received diuretics within 24 hours of blood sampling for AVP measurement are represented by open circles. Reprinted with permission (31).

increased in the hypothalamus of rats with chronic heart failure as compared to sham-operated controls. Therefore, in addition to the increased plasma levels of AVP, increased gene expression of AVP was shown to be associated with cardiac failure.

Bichet et al. (33) further investigated the relationship between cardiac function and non-osmotic release of AVP. They showed that patients with non-osmotic release of AVP had significantly lower cardiac indices, higher pulmonary capillary wedge pressures and higher plasma renin and aldosterone concentrations. When these patients were treated with an angiotensin converting enzyme (ACE) inhibitor, cardiac index increased significantly, suggesting amelioration of arterial underfilling. The reversal of arterial underfilling was associated with an improvement in urinary dilution and increased water excretion. Moreover, plasma and platelet AVP levels were significantly reduced following afterload reduction with the ACE inhibitor and improvement in cardiac output.

The V2 receptor is the antidiuretic receptor for AVP on the basolateral surface of the collecting duct, while the V1 receptor is the vascular smooth muscle receptor. In a rat model of cardiac failure, administration of a non-peptide V2 receptor antagonist has been shown to reverse the impaired water excretion (34). In a randomized, double-blind, placebo-controlled study, the orally active, non-peptide, selective V2 receptor antagonist, WAY-VPA-985, was used in humans with congestive heart failure (35). This agent decreased urine osmolality and increased urine flow, and serum sodium concentration.

Aquaporin-2 (AQP-2) is the AVP-regulated water channel that mediates water transport through the renal collecting duct. Activation of V2 receptors by AVP increases intracellular cyclic adenosine monophosphate (cAMP) level by activating adenylate cyclase. Subsequently, through activation of protein kinase A, cytoplasmic vesicles containing AQP-2 water channels "traffic" to the apical membrane of the collecting duct to make the membrane permeable to water. In the absence of AVP, endocytic retrieval of the AQP-2 water channels into the cytoplasm occurs and the membrane becomes impermeable to water. This phenomenon of the trafficking of AQP-2 water channels has confirmed the shuttle hypothesis (36).

Studies of rats with chronic heart failure have showed increased papillary AQP-2 protein expression (37, 38). This overexpression of AQP-2 decreased significantly when these rats were treated with the V2 antagonist, OPC-31260 (38). Moreover, this decrease was associated with the reversal of water retention in these animals.

It is known that about 3 – 6% of AQP-2 water channels that traffic to the luminal membrane of the collecting duct are excreted in the urine (39, 40). Thus, in the case of increased trafficking to the membrane, an increased level of AQP-2 can be detected in the urine. In this regard, Saito et al. (41) showed that when plasma AVP levels were increased with hypertonic saline, the urinary AQP-2 was increased in a linear manner. A recent study of hyponatremic heart failure patients demonstrated that treatment with a selective V2 receptor antagonist was associated with a dose-related increase in water excretion, correction of hyponatremia and a decrease in urinary AQP-2 excretion (Fig. 8) (42).

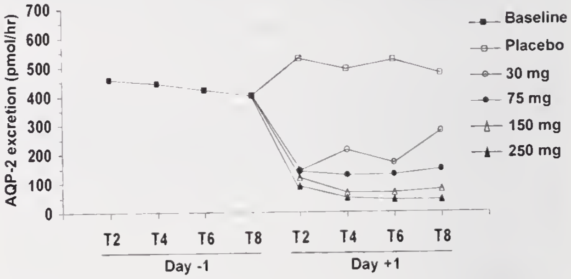

Fig. 8. Selective V2 receptor antagonism decreases 24-hour urinary aquaporin-2 (AQP-2) excretion in human heart failure. Reprinted with permission (42).

In normal subjects, high doses of aldosterone initially increase renal sodium retention. However, after an increase of 1.5 – 2 L of extracellular fluid volume, renal sodium retention ceases. This "escape" from the sodium-retaining action of aldosterone is due, at least in part, to an increased distal delivery of sodium to the site of action of aldosterone (19). However, patients with heart failure show an impaired escape from the effect of aldosterone because the activated neurohumoral mechanisms which maintain arterial pressure also decrease sodium delivery to the distal nephron (Fig. 9) (19). In this regard, the aldosterone antagonist, spironolactone, causes a marked natriuresis when given in sufficient doses to patients with heart failure (43).

In normal subjects, infusion of ANP causes increased natriuresis. However, patients with cardiac failure are resistant to this natriuretic effect of exogenously administered ANP (22). In patients with chronic heart failure, a linear

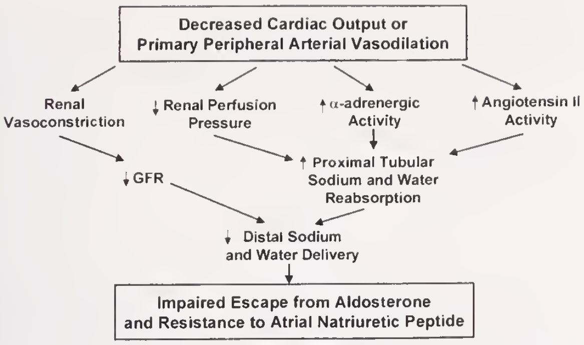
Decreased Cardiac Output or
Primary Peripheral Arterial Vasodilation
Renal Vasoconstriction
↓ Renal Perfusion Pressure
↑ α-adrenergic Activity
↑ Angiotensin II Activity
↓ GFR
↑ Proximal Tubular Sodium and Water Reabsorption
↓ Distal Sodium and Water Delivery
Impaired Escape from Aldosterone
and Resistance to Atrial Natriuretic Peptide

Fig. 9. A decrease in cardiac output or peripheral arterial vasodilation can initiate events that diminish distal sodium delivery, thereby impairing aldosterone escape and causing resistance to the natriuretic response of atrionatriuretic peptide (ANP). Reprinted with permission (19).

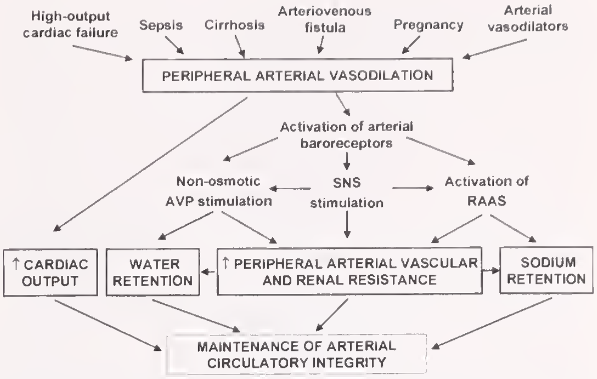
High-output cardiac failure
Sepsis
Cirrhosis
Arteriovenous fistula
Pregnancy
Arterial vasodilators
PERIPHERAL ARTERIAL VASODILATION
Activation of arterial baroreceptors
Non-osmotic AVP stimulation
SNS stimulation
Activation of RAAS
↑ CARDIAC OUTPUT
WATER RETENTION
↑ PERIPHERAL ARTERIAL VASCULAR AND RENAL RESISTANCE
SODIUM RETENTION
MAINTENANCE OF ARTERIAL CIRCULATORY INTEGRITY

Fig. 10. Sequence of events in which peripheral arterial vasodilation is the central initiator of renal sodium and water retention. SNS = sympathetic nervous system; RAAS = renin-angiotensin-aldosterone system. Reprinted with permission (26).

correlation was found between plasma concentrations of ANP and urinary excretion of cyclic guanosine monophosphate (cGMP), which is the intracellular secondary messenger of ANP (44). This finding suggests that the resistance to ANP is not at the receptor level in cardiac failure patients. Pettersson et al. (45) demonstrated that the resistance to ANP can be reversed after renal denervation in rats with heart failure. Since renal denervation decreases proximal tubular sodium reabsorption and thus increases distal sodium delivery, resistance to ANP in patients with cardiac failure is probably due to decreased distal sodium delivery to the collecting duct site of the hormone's action.

High-Output Cardiac Failure

Sodium and water retention occurs not only in low-output cardiac failure but also in high-output cardiac failure, e.g., thyrotoxicosis, beriberi and large arteriovenous fistulae. In conditions associated with high cardiac output, the reason for arterial underfilling is arterial vasodilatation (Fig. 10) (26).

Riegger et al. (46) showed that plasma renin, norepinephrine and AVP levels were elevated and plasma osmolality was decreased in a rat model of high-output cardiac failure secondary to an aortocaval fistula. These same compensatory neurohumoral responses occur in both high- and low-output cardiac failure. Thus, as proposed by the body fluid volume regulatory hypothesis, the trigger for arterial underfilling is decreased peripheral vascular resistance in high-output cardiac failure and decreased cardiac output in low-output cardiac failure (Fig. 11).

In advanced cardiac failure, the compensatory responses to arterial underfilling may lead to maladaptive consequences, which include pulmonary congestion, increased myocardial demand and increased cardiac afterload (Fig. 12). Understanding the pathophysiology of the vicious cycle of chronic congestive heart failure has led to various advances in treating heart failure patients (Fig. 13) (47). Myocardial injury causes depressed ventricular performance, which leads to reduced cardiac output. As a compensatory response to the reduced cardiac output, the SNS, the RAAS system and non-osmotic release of AVP are stimulated to maintain blood pressure. However, these responses lead to a vicious cycle, since the resulting systemic vasoconstriction and renal sodium and water retention increase ventricular pre- and afterload and myocardial hy-

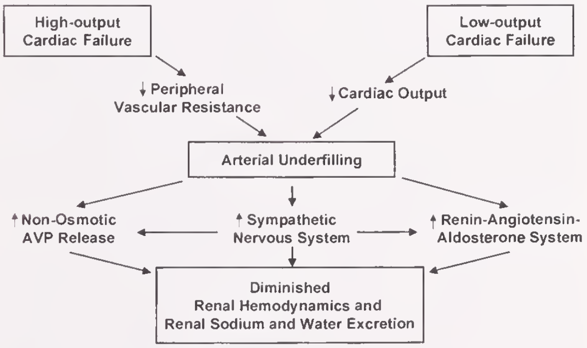
High-output Cardiac Failure
Low-output Cardiac Failure
↓ Peripheral Vascular Resistance
↓ Cardiac Output
Arterial Underfilling
↑ Non-Osmotic AVP Release
↑ Sympathetic Nervous System
↑ Renin-Angiotensin-Aldosterone System
Diminished Renal Hemodynamics and Renal Sodium and Water Excretion

Fig. 11. High-output and low-output cardiac failure. Although the initiating "underfill" event differs in high- and low-output failure, the subsequent compensatory pathways leading to renal sodium and water retention are similar. Reprinted with permission (12).

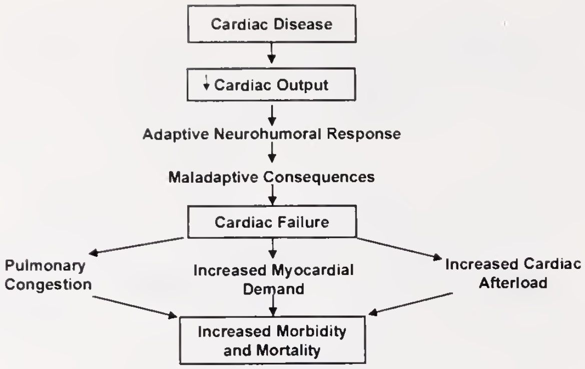
Cardiac Disease
↓ Cardiac Output
Adaptive Neurohumoral Response
Maladaptive Consequences
Cardiac Failure
Pulmonary Congestion
Increased Myocardial Demand
Increased Cardiac Afterload
Increased Morbidity and Mortality

Fig. 12. Compensatory responses become maladaptive in advanced cardiac failure. Reprinted with permission (28).

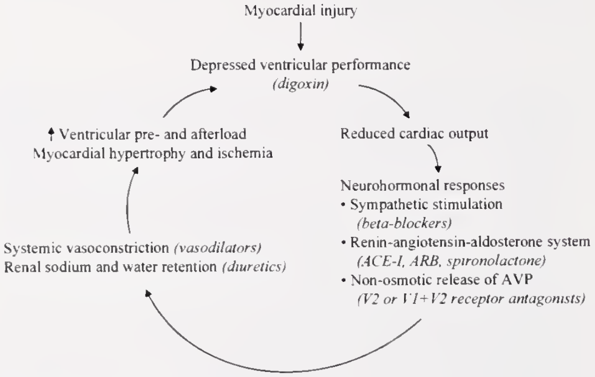
Myocardial injury
Depressed ventricular performance
(digoxin)
Reduced cardiac output
Neurohormonal responses
• Sympathetic stimulation
(beta-blockers)
• Renin-angiotensin-aldosterone system
(ACE-I, ARB, spironolactone)
• Non-osmotic release of AVP
(V2 or V1+V2 receptor antagonists)
Systemic vasoconstriction (vasodilators)
Renal sodium and water retention (diuretics)
↑ Ventricular pre- and afterload
Myocardial hypertrophy and ischemia

Fig. 13. Vicious cycle of depressed ventricular function. Potential therapies are in parentheses.
ACE-I = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; AVP = arginine vasopressin. Reprinted with permission (47).

pertrophy and ischemia, further decreasing myocardial performance.

In recent years, there have been major advances in the treatment of heart failure, directed toward the pathophysiological mechanisms (Fig. 13). Clinical studies have shown that ACE inhibitors improve survival not only in patients with cardiac failure (48, 49), but also in asymptomatic patients with left ventricular dysfunction (49). Moreover, ACE inhibitors significantly decrease the incidence of heart failure and cardiovascular death in patients with vascular disease but normal ejection fractions, and in diabetic patients with cardiovascular risk factors (50). Recent trials have showed that beta blockers are beneficial in reducing mortality in patients with cardiac failure (51 – 53). Another important advance in the treatment of cardiac failure is the finding that the aldosterone antagonist, spironolactone, significantly reduces morbidity and mortality in patients with severe heart failure (54). This effect of spironolactone appears to be extrarenal, perhaps by decreasing cardiac fibrosis. Vasodilators, diuretics and digoxin are the other classes of drugs that are being used in the treatment of heart failure.

Cirrhosis

The sodium and water retention in cirrhosis can also be explained by the unifying hypothesis of body fluid volume regulation, as is the case with low- and high-output cardiac failure. In both cardiac failure and cirrhosis, the kidney is responding in a similar manner to compensate for arterial underfilling.

For decades, there were two hypotheses to explain renal sodium and water retention in cirrhotic patients. According to the "underfilling hypothesis," portal hypertension leads to ascites formation, and the subsequent decrease in plasma volume causes the kidneys to retain sodium and water (55). However, when the plasma volume was measured in cirrhotic patients, it was found to be increased, and this increase in plasma volume antedated the ascites formation (56, 57). Thus, the "overflow hypothesis" was proposed; it suggested that a hepatorenal reflux mechanism is initiated in cirrhosis, whereby the kidneys retain sodium and water and cause plasma volume expansion and ascites formation (58). However, this "overflow" hypothesis does not explain the neurohumoral responses during the progression of cirrhosis. As cirrhosis progresses from the compensated to the decompensated (ascitic) phase, toward the hepatorenal syndrome, the neurohumoral responses are aggravated as a result of the increase in peripheral arterial vasodilation (Fig. 14) (58, 59). If primary plasma volume expansion (of both the venous and arterial compartments) occurs as suggested by the "overflow

	Compensated cirrhosis (no ascites)	Decompensated cirrhosis (ascites)	Hepatorenal syndrome
Peripheral arterial vasodilation	↑	↑↑	↑↑↑
Plasma hormones (AVP, renin, aldosterone, NE)	Normal	↑	↑↑
Plasma volume	↑	↑↑	↑↑↑

Fig. 14. Progressive hemodynamic and hormonal changes in cirrhosis. NE = norepinephrine. Reprinted with permission (59).

hypothesis," the plasma hormones of AVP, aldosterone and norepinephrine should be suppressed, not stimulated, as actually occurs with the progression of cirrhosis.

Since neither the "underfilling" nor the "overflow" hypothesis could totally explain the sodium and water retention in cirrhosis, the "peripheral arterial vasodilation hypothesis" has been proposed (60). According to this hypothesis, splanchnic vasodilation occurs early in the course of cirrhosis. The resulting arterial underfilling stimulates neurohumoral responses, which lead to renal sodium and water retention. This hypothesis explains the increased cardiac output and the enhanced neurohumoral changes over the entire spectrum of cirrhosis.

Recent studies using Doppler ultrasonography have demonstrated increased brachial, femoral, renal and cerebral vascular resistances in cirrhosis (61–63). However, the overall total systemic vascular resistance is decreased. Moreover, there is a correlation between the decrease in peripheral vascular resistance and the increase in plasma volume in cirrhotic patients (64). The central blood volume (i.e., the blood volume present in the central part of the circulation), which modulates the tone in the arterial and cardiopulmonary receptors, is decreased in cirrhosis (64). There is also a significant correlation between the decrease in central volume and the increase in portal venous pressure, as assessed by the hepatic venous pressure gradient (64).

Albillos et al. (65) studied rats with portal hypertension due to portal vein constriction to elucidate the relationship between portal hypertension, splanchnic vasodilation and sodium retention. In this study, systemic vascular resistance decreased within 24 hours of the constriction of the portal vein, and an increase in total body sodium was observed within 48 hours. These findings show that arterial underfilling due to arterial vasodilation precedes the sodium retention in portal hypertension.

La Villa et al. (66) administered large doses of mineralocorticoid to compensated cirrhotic patients, to investigate the characteristics of the patients who failed to "escape" from the sodium retaining effects of the hormone and thus developed ascites. The cirrhotic patients who failed to escape demonstrated significantly higher cardiac output and lower systemic vascular resistance (i.e., arterial underfilling) compared to those patients who demonstrated mineralocorticoid escape and did not develop ascites.

As with cardiac failure, the neurohumoral response correlates with the severity of the cirrhosis. Patients with the highest plasma renin and norepinephrine concentrations have the poorest survival rates (60). There is also a correlation between plasma norepinephrine and AVP concentrations, suggesting that the increased activity of the SNS stimulates the nonosmotic release of AVP (67). As in cardiac failure, the presence of hyponatremia in cirrhotic patients is associated with a poor outcome (68).

The bioassay method suggested that AVP could not be detected in hyponatremic cirrhotic patients, as was also noted in heart failure patients. However, after the development of the radioimmunoassay method, it was clearly shown that an acute waterload did not suppress plasma AVP in hyponatremic cirrhotic patients (69). In rats with experimental cirrhosis, the increased plasma levels of AVP are accompanied by increased expression of hypothalamic mRNA for AVP (70). The collecting duct AQP-2 mRNA expression is also significantly increased in cirrhotic animals as compared to controls (71). This high expression of AQP-2 was not suppressed with an acute waterload. However, its expression diminished significantly after the administration of a V2 receptor antagonist. Moreover, Tsuboi et al. (72) showed that the non-peptide AVP antagonist OPC-31260 significantly increased urine volume and decreased urinary osmolality in cirrhotic rats.

The effect of V2 receptor antagonists has been investigated in cirrhotic patients. An orally active, non-peptide V2 receptor antagonist has been shown to increase urine volume and decrease urine osmolality in patients with cirrhosis (73). Serum sodium concentrations can also be corrected in hyponatremic cirrhotic patients with these agents (74).

In order to investigate the role of V1 AVP receptors in liver disease, Claria et al. (75) administered a V1 receptor antagonist to cirrhotic animals, after the blockade of angiotensin II with saralasin. A decrease in blood pressure was observed, suggesting that AVP also plays a role in maintaining arterial circulatory integrity in cirrhosis, along with the RAAS and SNS.

Gregory et al. (76) showed that treatment with the aldosterone antagonist, spironolactone, was associated with weight loss and disappearance of ascites in a majority of patients with cirrhosis. This finding corroborates the important role of aldosterone in sodium retention in cirrhosis, and is compatible with the failure of cirrhotic patients to demonstrate mineralocorticoid escape.

The findings relative to plasma ANP in cirrhosis are very similar to those in heart failure patients. Skorecki et al. (77) showed, in cirrhotic patients, that the plasma ANP levels and urinary excretion of cyclic GMP were increased in response to head-out water immersion (HWI), a maneuver used to increase the central blood volume. However, no change was observed in urinary sodium excretion, suggesting a resistance to ANP. As in heart failure, resistance to the natriuretic and diuretic response to ANP was shown to be reversed when the kidneys were denervated in rats with experimental cirrhosis (78).

In a study by Abraham et al. (79), patients with cirrhosis showed a marked natriuresis when ANP was given together with mannitol. This natriuresis was associated with increased distal tubular sodium delivery, as assessed by lithium clearance, during the infusion of mannitol. The lithium clearance was increased in responders receiving ANP together with mannitol, whereas it was not increased in nonresponder cirrhotic patients. There was no difference in the increase of urinary cGMP excretion between responders and nonresponders, thus providing evidence against a collecting duct receptor defect. The results of this study in cirrhotic patients thus supported decreased distal delivery as a major factor contributing to ANP resistance in cirrhosis.

Nicholls et al. (80) investigated the response to the combined treatment of HWI and norepinephrine in cirrhotic patients. Mean arterial pressure increased by HWI and norepinephrine treatment, but not by HWI alone. This combined treatment was also associated with an increase in urinary sodium excretion. In another study, the ability to excrete an acute waterload over a 5-hour period was also shown to increase from 28% to 90% with the combined treatment of HWI and norepinephrine in hyponatremic cirrhotic patients (81). In these studies, there was a linear correlation between the water excretion and increment of systemic vascular resistance, further supporting the peripheral arterial vasodilatation hypothesis of sodium and water retention in cirrhosis.

We then proposed that nitric oxide, which is a very potent vasodilator, mediates the vasodilation of the splanchnic bed in cirrhosis. Specifically, the increment of blood flow in the physiologic splanchnic shunts due to portal hypertension would increase shear-mediated endothelial nitric oxide activity, which could lead to arterial underfilling. The endothelial nitric oxide synthase (eNOS) expression was indeed shown to be increased in the aortas and the mesenteric arteries of cirrhotic rats with ascites as compared to control animals (82). Oral administration of the nonspecific nitric oxide synthase (NOS) inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME), for one week was associated with reversal of the upregulated eNOS expression in the aortas and mesenteric arteries of these cirrhotic animals. The aortic expression of the secondary messenger of nitric oxide, cGMP, was also shown to decrease in cirrhotic rats with ascites after treatment with L-NAME (Fig. 15, lower panel) (82). The hyperdynamic circulation was reversed with L-NAME as systemic vascular resistance, cardiac index and mean arterial pressure were normalized (Fig. 15, upper panel) (83). Furthermore, plasma renin activity, plasma concentrations of aldosterone, AVP and ANP were decreased, sodium and water excretion was increased (Fig. 16) and hyponatremia was corrected with L-NAME treatment (82).

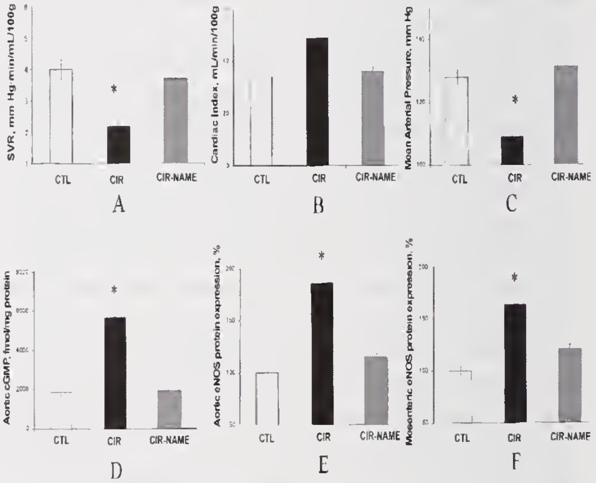

Fig. 15. **(A)** Systemic vascular resistance. **(B)** Cardiac index. **(C)** Mean arterial pressure. **(D)** Aortic concentrations of cGMP. **(E)** eNOS protein expression in aortas. **(F)** eNOS protein expression in mesenteric arteries. Chronic nitric oxide synthase (NOS) inhibition with 0.5 mg/kg/day L-NAME (CIR-NAME) for seven days by gavage increases systemic vascular resistance (SVR), decreases cardiac index, and increases mean arterial pressure. The concentration of cGMP and the expression of eNOS protein in the aorta and mesenteric arteries expression diminished in cirrhotic rats treated with L-NAME. Bars and segments represent the mean and the SEM, respectively. *P<0.01 versus untreated cirrhotic rats. CTL = control rats; CIR = rats with untreated cirrhosis; CIR-NAME = cirrhosis with L-NAME treatment; eNOS = endothelial nitric oxide synthase. Reprinted with permission (82, 83).

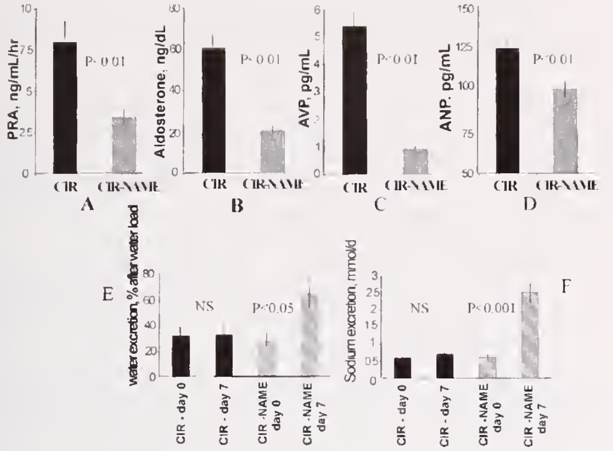

Fig. 16. **(A)** Plasma renin activity. **(B)** Aldosterone concentration. **(C)** AVP concentration. **(D)** ANP concentration. **(E)** Water excretion 3 hours following a water load of 30 mL/kg. **(F)** Sodium excretion. Concentrations of plasma renin, aldosterone, AVP and ANP decreased in cirrhotic rats with ascites with seven days of L-NAME treatment (CIR-NAME). Water and sodium excretion were impaired in both treated and untreated cirrhotic rats at day 0. After seven days of L-NAME a significant improvement in water and sodium excretion occurred in cirrhotic rats treated with L-NAME, but not in untreated cirrhotic rats. Bars and segments represent the mean and the SEM, respectively. PRA = plasma renin activity; AVP = arginine vasopressin; ANP = atrial natriuretic peptide; CIR = untreated cirrhosis; CIR-NAME = cirrhosis with L-NAME treatment. Reprinted with permission (82).

Spontaneous bacterial peritonitis (SBP) may occur as a complication in cirrhotic patients with ascites and is the most common cause of impairment in renal function in these patients (84). In this setting, the hyperdynamic circulation and arterial underfilling of cirrhosis worsens. A recent study showed that patients treated with intravenous albumin in addition to an antibiotic demonstrated a significant decrease in renal impairment and hospital mortality compared to patients treated with an antibiotic alone (85). Thus, an attenuation of the arterial underfilling by albumin administration altered mortality due to SBP.

Hepatorenal syndrome is a serious complication of cirrhosis, indicating an ominous prognosis. In a clinical study, the use of a V1 receptor blocker, terlipressin, together with albumin, was associated with a significant decrease in plasma renin activity and plasma norepinephrine (86). Most important, renal function improved and the hepatorenal syndrome was reversed with this treatment, which diminished the arterial underfilling and the resulting neurohumoral responses.

A recent randomized, prospective study compared therapeutic paracentesis with transjugular intrahepatic portosystemic shunt (TIPS) therapy in cirrhotic patients having refractory ascites (87). The result in this study differed from that in a previous study, which found no significant difference between the two treatments (88). However, unlike the earlier study, the more recent study included patients with better liver function (87). Thus, early reversal of portal hypertension with TIPS (e.g., Child-Pugh class B) may have a beneficial effect on decompensated cirrhotic patients with diuretic resistance.

Conclusion

Studies investigating the pathophysiology of sodium and water retention in cardiac failure and cirrhosis provided insights which have led us to the development of our unifying hypothesis of body fluid volume regulation. Treatment based on attenuation of the advanced responses to arterial underfilling by the sympathetic nervous system, the RAAS, and the non-osmotic release of AVP have been shown to benefit patients with cardiac failure and cirrhosis.

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Grand Rounds

Dopamine Receptors in Hypertension

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Abstract

There is increased awareness of the role of dopamine in cardiovascular function, renal function and systemic blood pressure regulation. Growing evidence indicates that each of the five dopamine receptor subtypes participates in the regulation of blood pressure by mechanisms distinct for that particular subtype. Some dopamine receptors regulate blood pressure by influencing the central and peripheral nervous system, while others influence renal function and release of renin, aldosterone and vasopressin. This review summarizes the physiology and pathophysiology of the peripheral dopaminergic system and our current understanding of the role of individual dopamine receptors in the pathophysiology of human essential hypertension.

Key Words: Hypertension, dopamine, dopamine receptor, sodium transport, transgenic mice.

Dopamine is now recognized as an important regulator of systemic blood pressure (1). In the periphery, this blood pressure regulation is achieved by direct action on the heart, arterial and venous vessels, to alter renal hemodynamics, and on fluid and electrolyte balance via effects on renal epithelial transport, and gastrointestinal sodium uptake (2–6). Dopamine can indirectly regulate blood pressure via release of hormones and humoral agents such as aldosterone, catecholamines, endothelin, prolactin, pro-opiomelanocortin, renin, and vasopressin (2–5). Centrally, dopamine modulates systemic blood pressure through the regulation of fluid and sodium intake via "appetite" centers in the brain (7). In addition, it controls blood pressure by direct action on neuronal cardiovascular centers.

Dopamine Receptors

Dopamine exerts its actions via the D_1-like and D_2-like family of cell-surface G protein-coupled receptors (GPCR) (Tables 1 and 2). The D_1-like receptors cloned in mammals (D_1 and D_5) are linked to the stimulatory G-protein, Gs, and stimulate adenylyl cyclases. The cloned D_2-like receptors (D_2, D_3, and D_4) are linked to inhibitory G-proteins, Gi/Go, and inhibit adenylyl cyclases. The affinity of dopamine to its receptors ranges from low nanomolar to low micromolar range. At higher concentrations, α- and β-adrenergic and serotonin receptors are occupied. Circulating concentrations of dopamine (picomolar range) are not sufficiently high to activate dopamine receptors, while in dopamine-producing tissues concentrations in the high nanomolar to micromolar range can be attained (1). Dopamine is synthesized not only in noradrenergic and dopaminergic nerves, but also in non-neural tissues (e.g., kidney, gastrointestinal tract) (8).

Autocrine/Paracrine Regulation of Fluid and Electrolyte Balance by Dopamine

Renal Sodium Transporters

Dopamine regulates water and electrolyte excretion indirectly by actions on renal hemodynamics and by modulation of the action of other vasoactive and renoactive hormones (1).

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TABLE 1

Summary of the Physiologic and Pathophysiologic Effects of D_1-like Receptors in Blood Pressure Regulation.

Dopamine Receptors	Signal Transduction	Characteristics of Transgenic Animals	Physiologic Responses	Implications in Human Essential Hypertension
D_1-like receptor family	G_{as} stimulation of Adenylyl cyclase (1,75,76) Phospholipase A_2 and eicosanoid formation (22, 24) Phosphatidyl-inositol 3 kinase (77)		Vasorelaxation (1, 2, 45) Decrease sodium and phosphate transport (kidney and intestine) (1, 2, 6, 9–15, 20–25, 27–33, 43, 48, 77).	Uncoupling of renal D_1 receptors from effector enzyme complex (52)
D_1 receptor	Stimulation of Phospholipase C* (78, 79)	D_1 knockout mice (48) Hypertension Sodium retention?	Stimulation of renin secretion (67) Natriuresis (49)	D_1 receptor non-coding region associated with hypertension (53)
D_5 receptor	Inhibition of Phospholipase C (80)	D_5 knockout mice (58, 59) Hypertension Increased central oxytocin/V_1/non-NMDA/α-adrenergic receptor activity	?	D_5 receptor locus linked to hypertension (60)

*Needs the adaptor protein calcyon (81).

TABLE 2

Summary of the Physiologic and Pathophysiologic Effects of D_2-like Receptors in Blood Pressure Regulation.

Dopamine Receptors	Signal Transduction	Characteristics of Transgenic Animals	Physiologic Responses	Implications in Human Essential Hypertension
D_2-like receptor family	Gαi/O inhibition of Adenylyl cyclase (1, 75, 76)		Vasorelaxation (when basal tone is high) (2, 82, 83) Vasoconstriction (when basal tone is low) (2, 84, 85) Inhibition of neural catechol and renin release (2) Increase sodium transport* (kidney and intestine) (34, 35, 84)	Central D_2-like function decreased in hypertension (61)
D_2 receptor		D_2 knockout mice (66) Increased activity of α-adrenergic and ETB receptors		D_2 receptor polymorphism associated with hypertension (64)
D_3 receptor	Phosphatidyl inositol 3 kinase (86)	D_3 knockout mice (70) Hypertension Renin-dependence Sodium retention?	Inhibition of renin secretion (70, 73) Increase in GFR (87)	?
D_4 receptor		D_4 knockout mice Unknown	Inhibition of V_2 receptor action in cortical collecting duct (18)	?

*In concert with D_1-like receptors, sodium transport is decreased when extracellular fluid volume is moderately expanded (33, 88).

Direct actions of dopamine on renal tubules are mediated by multiple mechanisms. In proximal tubules, D_1-like receptors inhibit Na^+/H^+-exchanger 3 activity (NHE3) and Na/phosphate (Pi)-co-transporter activity in the luminal membrane, and Na^+/HCO_3^--cotransporter activity in the basolateral membrane (1, 9–13). In addition, D_1-like receptors inhibit Na^+/K^+-ATPase activity in the proximal tubule, medullary thick ascending limb of Henle (mTAL), and cortical collecting duct (CCD) (14–16). D_1-like receptors can also regulate sodium channels, although this action has not been shown in the kidney so far. The ability of dopamine to inhibit tubular transport in multiple nephron segments may explain the marked natriuretic effect of dopamine in spite of its limited inhibitory effect on individual sodium transporters.

In renal proximal tubules, D_2-like receptors stimulate sodium transport through an increase in NHE3- and Na^+/K^+-ATPase activity, an effect which is mediated mainly by a decrease in cAMP production (1, 9, 17). In the CCD and the medullary collecting duct (MCD), D_2-like receptors antagonize the actions of aldosterone and vasopressin (18, 19).

Signal Transduction Pathways

The inhibitory action of D_1-like receptors on NHE3- and Na^+/HCO_3^--cotransporter activities in renal proximal tubules is mainly due to activation of the cAMP/protein kinase A (PKA) and eicosanoid pathways (1, 9, 20). The contribution of D_1 and/or D_5 receptors in these actions remains to be determined. Dopamine can also inhibit NHE3- and Na/Pi-cotransporter activity by activating a G protein-linked pathway independent of PKA, protein kinase C (PKC), eicosanoids, and protein tyrosine kinase (11, 12, 21). The signal transduction pathways of dopamine-mediated inhibition of Na^+/K^+-ATPase activity are complex. It is nephron segment specific, time dependent, and intracellularly calcium modulated (1). Thus, only PKA may be needed to transduce the D_1-like signal in the mTAL and CCD while PKA, PKC, and eicosanoids [20-HETE] are involved in the proximal tubule (22–25). Furthermore, phosphatidyl-inositol 3 kinase may be involved in the dopamine-mediated inhibition of Na^+/K^+-ATPase and NHE3 (26, 27) (Table 1).

D_1- and D_2-like Effects on Fluid and Electrolyte Balance

Some actions of dopamine appear to be counterregulatory (e.g., D_1-like inhibition of sodium transport and D_2-like stimulation of sodium transport, D_1-like receptor stimulation of renin and vasopressin secretion, D_2-like receptor inhibition of renin and aldosterone secretion). Increasing evidence suggests that the state of overall sodium balance determines which dopamine receptor subtype function predominates. The natriuretic effect of dopamine can be seen under conditions of "normal" sodium intake; it is magnified under conditions of "moderate" sodium excess (1). In sodium-replete states, endogenous renal dopamine is responsible for more than 50% of sodium excre-

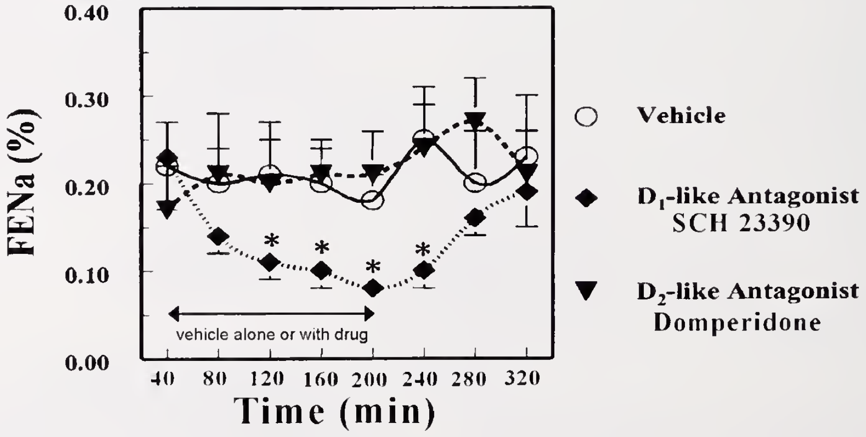

Figure. Effect of the D_1-like antagonist, SCH 23390, the D_2-like antagonist (domperidone), or vehicle on urinary fractional sodium excretion (FENa) in pentobarbital-anesthetized normotensive Wistar Kyoto (WKY) rats. WKY rats were given a saline load (5% of body weight). After a baseline period, the vehicle alone, or with the indicated antagonist, was given intravenously (SCH 23390, 400 ng/kg/min; domperidone, 1 g/kg/min) for four periods followed by three periods of recovery. Each period lasted 40 minutes.
*$P<0.05$ vs baseline period, repeated measures analysis of variance, Scheffe's test.
*$P<0.05$ vs others, analysis of variance, Scheffe's test (adapted from 33).

tion (28 – 32) (Figure). D_1-like receptors, independent of D_2-like receptors, can inhibit NHE3- and Na^+/HCO_3^--cotransporter activities. However, in sodium-replete states, D_1- and D_2-like receptors, rather than acting in opposing directions, synergistically inhibit Na^+/K^+-ATPase activity and increase sodium excretion (23, 33). The mechanism by which this occurs is unknown. An increased renal production of dopamine as well as an increased inhibitory effect of dopamine on sodium transporters might be involved (1). Alterations in dopamine receptor expression and effector protein functions (adenylyl cyclase, phospholipase C, sodium transporter/pump) do not explain the synergism between D_1- and D_2-like receptors in sodium-replete states (1). However, sodium-induced decreases in the concentrations of humoral factors that oppose D_1-like receptor action (e.g., angiotensin II, adenosine, serotonin) may play a role in sodium reabsorption and in renal hemodynamics (1). Sodium loading, for instance, attenuates the stimulatory effect of D_1-like receptors on renin release and enhances the D_2-like inhibitory effect on aldosterone secretion (and possibly renin). Moreover, during volume expansion, D_4 receptors may facilitate diuresis and natriuresis by antagonizing the hydro-osmotic and sodium retaining effect of vasopressin and aldosterone in the CCD (18, 19). Under conditions of positive sodium balance, dopamine not only increases renal water and electrolyte excretion but also decreases gastrointestinal water and electrolyte absorption.

When sodium loading is excessive, the natriuretic effect of dopamine is no longer evident, presumably because other natriuretic factors predominate (1, 29, 32). In addition, the inhibitory effect of endogenous dopamine on renal and gastrointestinal sodium transport is lost during hydropenia and sodium-deplete states (1, 28). Under conditions of negative sodium balance, D_2-like receptors may actually increase sodium reabsorption in the renal tubule and gastrointestinal tract and stimulate sodium appetite (7, 34, 35). When endogenous renal tubular dopamine subserves a paracrine/autocrine function, its natriuretic effect is mainly due to tubular rather than glomerular or renal hemodynamic action (1). However, dopamine produced by renal nerves may participate, via D_3 receptors, in the regulation of glomerular filtration rate, especially with the hyperfiltration that occurs during amino acid infusion (36).

Regulation of Blood Pressure by Dopamine

Dopamine regulates blood pressure by several mechanisms (2). In addition to dopaminergic regulation of fluid and electrolyte balance, dopamine regulates central cardiovascular centers and catecholamine release by sympathetic nerves and adrenal medulla (1). Direct and indirect actions of dopamine receptors can cause vasorelaxation (D_1 and D_5) or vasoconstriction (D_3) (2). At higher concentrations (high micromolar range), dopamine produces vasoconstriction by occupation of α_1-adrenergic receptors. These apparently counterregulatory actions are influenced by the basal tone of the vascular smooth muscles. When basal arterial tone is high, D_2-like receptors promote relaxation; the opposite action occurs when basal tone is low. Dopamine increases cardiac output by stimulating myocardial β-adrenergic receptors. The heart also expresses D_1 and D_4 receptors, but their role, if any, on heart rate or myocardial contraction remains to be determined (37, 38).

Dopamine and Hypertension

Abnormalities in dopamine production and receptor function have been described in genetic hypertension, and there is abundant evidence that, in the absence of a normally functioning dopaminergic system, hypertension develops (1 – 3, 13 – 15, 24, 25, 31, 39). Inhibition of dopamine synthesis outside the central nervous system accelerates the development of hypertension in the spontaneously hypertensive rat (SHR) (40). Moreover, dopamine receptor blockade is associated with the development of hypertension in saline-loaded Wistar rats and potentiates the renal effects of nitric oxide inhibition in humans (41, 42). Finally, disruption of dopamine receptor genes in mice produces hypertension (see below) (Tables 1 and 2).

D_1-like Receptors

The renal autocrine/paracrine natriuretic function of dopamine via D_1-like receptors is impaired in genetic hypertension of rodents (SHR and Dahl salt-sensitive rat) (1, 2). This impairment is not caused by a decreased renal dopamine production but by a diminished D_1-like inhibition of NHE3, Na^+/HCO_3^-, and Na^+/K^+-ATPase activity in proximal tubules and the mTAL (1, 2, 13 – 15, 24, 25, 43). Recent data indicate that the failure of D_1-like receptors to inhibit sodium transport in genetic hypertension is not caused by abnormalities in G-proteins or effector proteins (adenylyl cyclases, NHE3, $Na^+/K^+ATPase$), or the expression of D_1-like receptors. Rather, the D_1-like receptor is uncoupled from its G protein/effector protein complex (1, 2, 13–15, 24, 25, 43–45). The reason for the uncoupling of the D_1-like receptor from its G protein/ effector protein complex is currently unknown, but abnormalities in the desensitization process of D_1-like receptors might be involved (see below). There is evidence that the uncoupling of D_1-like receptors in hypertension is genetically determined, and receptor-, organ-, and nephron-segment specific (1, 2). This explains why the vasodilatory and "distal" renal tubular responses to D_1-like agonists are preserved even in hypertensive subjects (46, 47).

D_1 receptor. Because the major receptor involved in the dopamine-mediated natriuresis is the D_1 receptor (1, 26, 48, 49), we have suggested that the renal dopaminergic defect in genetic hypertension probably involves the D_1 rather than the D_5 receptor. The D_1 receptor locus is linked to variations in systolic blood pressure levels in Caucasians (50) and cardiac hypertrophy in rats (51). Disruption of the D_1 receptor in mice leads to the development of hypertension (48). However, no mutations have been found in the coding region of the D_1 receptor in patients with essential hypertension or in genetically hypertensive rats (1, 52). A polymorphism in the noncoding region of the D_1 receptor has been reported to be associated with human essential hypertension; however, the mechanism by which this polymorphism induces hypertension remains to be determined (53).

We have suggested that the uncoupling of D_1 receptor from its effector complex in renal proximal tubules is due to a ligand-independent serine phosphorylation and subsequent desensitization of the D_1 receptor (52). Because G protein-coupled receptor kinases (GRKs) phosphorylate GPCRs, resulting in their desensitization, it is of interest that total GRK activity and GRK2 expression are increased in lymphocytes of patients with essential hypertension and in lymphocytes and aortic smooth muscle cells of rats with genetic hypertension (54, 55). However, it is unlikely that GRK2 is the proximate cause of the D_1 receptor desensitization, because the parathyroid hormone receptor, a substrate of GRK2, functions normally in hypertension (1, 2, 52). Thus, the desensitization of the D_1 receptor in hypertension may be due to a kinase other than GRK2. A kinase related to GRK that interacts with genes controlling the renin-angiotensin system may be involved in the hypertensive process (56). The uncoupling of the D_1-like receptor in renal proximal tubules in hypertension may also be a consequence of a defective resensitization process (57).

D_5 receptor. The other D_1-like receptor, the D_5 receptor, may also play a role in the pathogenesis of genetic hypertension. Disruption of the D_5 receptor gene in mice results in the development of hypertension without an impairment in the ability to excrete an acute saline load (58). We have suggested that the hypertension in D_5 receptor mutant mice is caused, in part, by interactions of the D_5 receptor with other GPCRs utilizing a common pathway in the central nervous system. The high blood pressure in the D_5 receptor knockout mouse was normalized by blockade of V_1-vasopressin, and α-adrenergic receptors (59). Furthermore, the hypertension in D_5-receptor mutant mice was antagonized by a non-NMDA receptor antagonist that crosses the blood-brain barrier, while a non-NMDA receptor antagonist that does not cross the blood-brain barrier had no effect on blood pressure (59). This indicates that non-NMDA receptors are involved in the signal transduction pathway of D_5 dopamine receptors in the brain. Although mutations of the D_5 receptor are not found in the SHR (unpublished data), a locus in human chromosome 4 containing the D_5 receptor gene has been linked to hypertension in some populations with essential hypertension (60).

D_2-like Receptors

D_2 receptor. Abnormalities of D_2-like receptor function have been reported in hypertension (3, 61–63). Several D_2 receptor polymorphisms have been reported, one of which is associated with hypertension (64). Transfer of a segment of chromosome 8, containing the D_2 receptor gene, from the normotensive Brown-Norway rat onto SHR background decreases blood pressure (65). Disruption of the D_2 receptor gene in mice produces hypertension that is not associated with a decreased ability to excrete a sodium load. Rather, the hypertension in D_2 receptor knockout mice is caused by increased activity of the adrenergic nervous system (66). An unexpected finding in D_2 knockout mice was the ability of an endothelin B (ETB) antagonist (BQ788) to normalize the blood pressure in the D_2 mutant mice without affecting blood pressure in D_2 wild type mice.

Dopamine, dopamine receptors, endothelin, and ETB receptors have been found in brain and spinal regions known to control cardiovascular function (3).

D_3 receptor. Renin secretion in rats is stimulated by D_1-like receptors and inhibited by D_2-like receptors (1, 67). Both D_1- and D_2-like receptors downregulate AT_1 receptor expression and function (68, 69). Disruption of the D_3 receptor gene in mice is associated with renin-dependent hypertension and a decreased ability to excrete an acute saline load (70). Aberrant dopaminergic regulation of aldosterone secretion (via D_3 receptors) may be involved in some forms of hyperaldosteronism and hypertension (71, 72).

D_4 receptor. D_4 receptors are expressed in rat juxtaglomerular cells and cortical and medullary collecting ducts (73). However, the consequence of disruption of the D_4 receptor gene on blood pressure has not been reported.

Conclusions

Dopamine regulates fluid and electrolyte balance by direct and indirect actions in the kidney, blood vessels, gastrointestinal tract, adrenal glands, sympathetic nervous system, hypothalamus and other "brain centers." Dopaminergic regulation of the secretion of angiotensin and aldosterone, catecholamines, and vasopressin contributes to this process. Furthermore, dopamine can also regulate the expression of receptors other than its own (e.g., ETB, AT_1). Abnormalities of dopamine receptors (or their regulation) may be important in the pathogenesis of essential hypertension. The pathogenetic pathway of hypertension is specific for each type of dopamine receptor abnormality (Tables 1 and 2). The dopaminergic system is, phylogenetically, an old system (74), which may serve to regulate blood pressure.

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Near-Fatal Pulmonary Embolism

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Abstract

A case of a 79-year-old female admitted to the hospital with a hip fracture and suffering a near-fatal embolism, is presented. The article then reviews the epidemiology of deep venous thrombosis and pulmonary embolism in the setting of hip fracture and orthopedic surgery and outlines the diagnostic approach to a critically ill patient with pulmonary embolism. The use of thrombolysis as an adjunct to usual heparin therapy is examined, as are the potential benefits versus the absolute risks of thrombolysis. Finally, practical recommendations outlining a reasonable approach to this group of patients, based on available evidence, are proposed.

Key Words: Pulmonary embolism, thrombolytic therapy, echocardiography.

Case Presentation

A 79-YEAR-OLD FEMALE with a history of hypertension, diabetes, Parkinson's disease and colon cancer was admitted to the orthopedic service with a traumatic right femur fracture. The patient underwent an uneventful right hip reduction and internal fixation on the third hospital day. She received one dose of warfarin on the evening of the first postoperative day. The following evening the patient developed shortness of breath, and intravenous heparin was administered. But the patient continued in severe respiratory distress, responding only to noxious stimuli. Examination revealed blood pressure of 90/60 mm Hg, respiratory rate of 40/min, and regular heart rate of 90 beats per minute. Oxygen saturation with 100% oxygen by facemask was 90 – 95%. She had central cyanosis. There was no obvious jugular venous distention, and the mucus membranes were moist. Her pupils were equal and reactive to light, the heart was normal, and the lungs were clear bilaterally. Her extremities were cyanotic and cool, with thready pulses. There were no palpable lower extremity venous cords or petechiae, and the surgical wound was clean and dry. Electrocardiogram revealed a regular sinus rhythm (rate of 83/min), a left axis deviation and a left anterior fascicular block unchanged from the admission tracing.

She deteriorated, becoming hemodynamically unstable with a palpable blood pressure of 60 mm Hg. She was treated with aggressive fluid resuscitation. Arterial blood gas analysis obtained while the patient was breathing 100% inspired oxygen revealed a pH of 7.38, carbon dioxide tension 24.7 mm Hg, and P_aO_2 of 82 mm Hg (100% saturation). Serum lactate, white blood count and creatinine were elevated. Serum creatine phosphokinase (CPK) and lactic dehydrogenase (LDH) were both markedly elevated, but creatine kinase MB band (CK-MB) was normal.

She remained hypotensive despite administration of 1.5 liters of normal saline. Oxygen saturation decreased and she appeared pre-terminal. A presumptive diagnosis of massive pulmonary embolism (PE) was made. The heparin drip was discontinued and tissue plasminogen activator (TPA) was administered as a 15-mg bolus, followed by an 85-mg infusion over 90 minutes. Within 30 minutes the oxygen saturation improved and blood pressure rose to 100/70, with overall improvement in the patient's clinical status. Ninety minutes following infusion of TPA, the arterial blood gas was P_aO_2 = 166 mm Hg. She was transferred to the med-

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ical intensive care unit. By the next morning she was stable, breathing room air comfortably. Her chest radiograph showed cardiomegaly with no pulmonary infiltrates or effusions. Repeat hemoglobin revealed a significant drop (3 grams). She was transfused and heparin was withheld until her prothrombin time normalized and her partial prothrombin time was twice control value. A head computed tomography (CT) without contrast was obtained because of some residual confusion; no hemorrhage was seen. She returned to her nursing home.

Introduction

The object of life is not to be on the side of the majority, but to escape finding oneself in the ranks of the insane.

Marcus Aurelius

The use of thrombolytic therapy in the treatment of pulmonary embolism remains controversial. Contraindications include the immediate postoperative period, active bleeding, new neurological findings, and advanced age. Advocates of thrombolytic therapy for thromboembolic disease generally recommend some laboratory confirmation of the diagnosis prior to therapy. The decision to empirically treat this desperately ill, elderly patient with a history of hypertension, one day after hip surgery, was difficult. A therapeutic failure or life-threatening complication would certainly have occasioned a majority view that use of thrombolysis in this patient was unwise. Clinical acumen, an accurate risk-benefit analysis, and the courage to treat despite major contraindications led to an excellent clinical outcome.

Epidemiology

Despite advances in the diagnosis and treatment of deep venous thrombosis and pulmonary embolism (DVT-PE), only 260,000 of the projected 600,000 cases per year of DVT-PE are correctly diagnosed (1). This results in significant morbidity and mortality (30%) (2). Investigators (3) have documented readily identifiable risk factors that define patients and patient populations at high risk for venous thromboembolism. The top six risk factors are advanced age, obesity, history of previous DVT-PE, cancer, bedrest and major surgery. The patient in this report had at least three of these six risk factors and therefore a 50% likelihood of pulmonary embolism based on history alone (Table 1) (4).

TABLE 1

Proportion of Patients with Clinically Suspected DVT in Whom Diagnosis Was Confirmed by Objective Testing Increases with the Number of Risk Factors.

Number of DVT Risk Factors	Objectively Confirmed DVT (%)
0	11
1	24
2	36
3	50
4 or more	100

Data from Wheeler HB, Anderson FA, Cardullo PA, Jr, et al., modified with permission (4).

Considerable work has been done on attenuating the impact of risk factors in those patients at highest risk (5–7). Unfortunately, despite the longstanding evidence of the efficacy of various prophylactic agents, the adequacy of physician practices remains in question (8). Stasis, intimal injury and hypercoagulability (Virchow's triad) are the three underlying physiologic tenets that define risk for the development of DVT-PE. "Stasis" results from the supine position and the effects of general anesthesia that begin and can be readily identified within the operating theater (9, 10). "Intimal injury" results from mechanical trauma (ligatures, tourniquets, vessel traction) and humoral factors associated with stress (vasoactive amines), excessive free radical generation and anesthetic agents (11, 12). This constellation promotes "hypercoagulability" secondary to venous stasis and decreased clearance of activated clotting factors. Numerous clotting factors have been examined, including fibrinopeptide A, platelet factor 4, D-dimers, antithrombin III, prothrombin factor 4 tissue plasminogen activator inhibitor, and decreased plasmin activity (13). None of these factors, however, have arisen as either specific or sensitive assays to aid in identifying those surgical patients at greatest risk for the development of DVT-PE. Therefore, it is prudent for the practitioner to determine clinical risk factors, stratify overall risk and provide prophylaxis accordingly (14). Patients should be classified as having low, moderate, high or very high risk for developing DVT-PE (Table 2).

This patient had a traumatic hip fracture followed by orthopedic surgery. The American College of Chest Physicians Consensus Conference on Antithrombotic Therapy (5) strongly advocates prophylaxis for DVT-PE in this surgical group. Hip fractures have been shown to

TABLE 2
DVT and PE Risk Classification.

Risk Categories	Calf DVT (%)	Proximal DVT(%)	Fatal PE (%)
Low Age <40 years, minor surgery, no secondary risk factors*	2	<0.4	<0.002
Moderate Age >40 years, major surgery, no secondary risk factors*	10–20	4–8	0.1–0.4
High Age >40 years, major surgery, secondary risk factors age >60 years, major surgery, no risk factors	20–40	4–8	0.4–1
Very High age >40 years, major surgery, previous DVT, PE, cancer, hypercoagulable state, orthopedic surgery, multiple trauma, acute SCI	40–80	10–20	1–5

*Secondary risk factors: Obesity, varicose veins, estrogen use, malignancy, immobilization, and paralysis. SCI = spinal cord injury. Data from Clagett GP, Anderson FA, Jr, Geerts W, modified with permission (14).

have a DVT-PE incidence of 40–45% with fatal pulmonary embolism occurring in as many as 6–10% of those who have surgical repair (15, 16). External pneumatic compression devices, warfarin sodium, adjusted dose unfractionated heparin (UFH) and low molecular weight heparin (LMWH) have all been shown to be more effective than low-dose heparin or no prophylaxis after elective hip surgery (17). External compression, though effective, needs to be utilized 23 hours per day and is not practical, given shortened hospital stays and early mobilization. In hip fracture repair, "preoperative" adjusted dose warfarin has been shown since 1959 (15) to result in reductions in incidence of both DVT (27% to 3%) and fatal PE (10% to 0%). The patient in this report received no preoperative prophylaxis; warfarin was administered only on the first postoperative day. The clinical risks for developing DVT-PE were considerable for this patient, and prophylaxis was inadequate.

Diagnostic Approach

The approach to the acutely ill patient with pulmonary embolism is essentially the same as for the general population, with certain caveats. The physician must balance the need to make a quick and accurate diagnosis with providing prompt, life-saving treatment. Treatment is often begun prior to establishing a definitive diagnosis. Ventilation-perfusion scanning generally is still considered the procedure of first choice. However, disadvantages include low sensitivity (18), general unavailability "after hours," and the fact that it is time consuming. Unstable patients (hypoxia, hemodynamics) may not be able to tolerate being transported to nuclear medicine departments for any extended interval of time.

The plasma D-dimer determination has received increasing interest as a screening test for DVT-PE, particularly when combined with clinical decision modeling and other diagnostic tests (19). However, the negative predictive value in patients clinically deemed to be at highest risk assessment for DVT-PE is not well known. Dynamic, contrast-enhanced, computerized tomographic angiography (spiral or helical CT) is a rapid, noninvasive means to diagnose patients with pulmonary embolism. Preliminary reports suggest good sensitivity and specificity with acceptable clinical outcomes (20–22). Departments of radiology routinely care for critically ill patients, and new, high-speed scanners allow for rapid scanning with single breath-holds that can even be performed in the ventilated patient.

The patient presented here is an example of the unstable patient for whom transportation is not feasible or safe, and for whom rapid, lifesaving bedside decisions are mandatory. While some bedside diagnostic tests can be effective, portable perfusion scans are cumbersome and offer limited views; the diagnostic accuracy compared to traditional ventilation perfusion scanning is not well characterized. Bedside echocardiography is extremely valuable, both as a diagnostic tool and as a predictor of clinical outcomes (23, 24). Transthoracic echocardiography is simple, noninvasive and readily available, but subject to limitations of image quality and subjective interpretations. Transesophageal echocardiography is much more accurate in visualizing the right-sided cardiac chambers, providing accurate assessment of right ventricular pressure overload, hypokinesis and ventricular wall motion abnormalities. However, it is relatively invasive and requires an experienced operator. Echocardiography offers the additional advantage of confirming alternative diagnoses such as myocardial infarction, acute aortic dissection or pericardial tamponade (which can masquerade as an acute pulmonary embolus). Finally, for a patient with multiple medical problems who is desperately ill, and who has contraindications to anticoagulation therapy, pulmonary angiography may remain feasible, though often not practical. Pulmonary angiography in unstable patients is difficult, requiring expertise in critical care management and interventional radiology. Angiography can be combined with therapeutic interventions such as catheter directed thrombolysis and placement of a vena caval filter device. Newer, catheter-based techniques offer the hope of *in situ* lysis (angiojet) of acute clots.

Recent studies of seemingly hemodynamically stable patients demonstrate a significant proportion of patients with echocardiographic evidence of right ventricular compromise and adverse clinical outcomes (24), despite appropriate standard care with unfractionated heparin (UFH). It has been suggested that, in this group of patients, thrombolytic therapy may result in fewer adverse events. The echocardiogram, therefore, aside from providing diagnostic information (e.g., pulmonary artery clot, isolated right ventricular pressure overload in high suspect cases), can aid in directing treatment beyond standard care. Deciding which patients with PE should have bedside echocardiography is difficult. While hemodynamically unstable patients are obvious candidates, Goldhaber has demonstrated right ventricular dysfunction in patients without obvious hemodynamic instability (24). Studies have shown that patients with less than 30% perfusion defects, as defined on nuclear perfusion scan, do not have echocardiographic evidence of right ventricular dysfunction (25). Therefore, a perfusion scan with greater than 30% decrement in perfusion is a sensitive, though nonspecific, screen for determining who should receive bedside echocardiography.

Thrombolysis as an Adjunct to Standard Care?

Anticoagulation with UFH remains the treatment of choice for patients presenting with an acute pulmonary embolus (26–28). Heparin therapy prevents further clot deposition and allows for natural fibrinolysis of the existing clot. Heparin anticoagulation provides secondary prevention of recurrent PE but does not provide primary therapy (lysis) of the acute embolism. Despite appropriate UFH care, there are patients who experience recurrent pulmonary emboli and mortality (29, 30). The Urokinase Pulmonary Embolism Trial (UPET) revealed that 15% of patients with massive PE had two or more previous episodes, and 20% of treated patients were found to have signs of recurrent PE within the first two weeks (29, 30). Clearly a substantial population of patients remains at risk, and adjunct therapies should be considered.

Thrombolytic agents dissolve clots promptly (31), hasten pulmonary reperfusion, reverse right heart failure (24) and improve capillary blood volume (32). Table 3 outlines the FDA-approved thrombolytic regimens. Intravenous TPA, compared with the other thrombolytic agents streptokinase and urokinase, achieves a faster clot lysis with improved safety and better tolerance, and is the most convenient fibrinolytic to administer (33). Therapeutic goals for thrombolysis should include symptom relief, hemodynamic stability, improvement in

TABLE 3
FDA-Approved Thrombolytic Regimens for PE.

Streptokinase: 250,000 IU as a loading dose over 30 minutes, followed by 100,000 U/hr for 24 hours — approved in 1977

Rt-PA: 100 mg as a continuous peripheral intravenous infusion administered over 2 hours — approved in 1978

Urokinase*: 4400 IU/kg as a loading dose over 10 minutes, followed by 4400/kg/hr for 12–24 hours — approved in 1978 pulmonary reperfusion (normalization of V/Q mismatch), improvement in right ventricular function and decreased mortality. However, there has been no randomized controlled trial that demonstrates a mortality benefit favoring thrombolytic therapy for PE. This fact, however, needs to be put in both historical and statistical context. The use of thrombolytic therapy for myocardial infarction goes back several decades. Early experience focused on demonstrating surrogate markers of mortality. Specifically, evidence of reperfusion, including improvement in coronary angiograms, left ventricular function, and constraint of infarct size served as early signs of efficacy until the large controlled trials were able to demonstrate survival benefit. The largest prospective, controlled PE thrombolysis trials (24, 30) do not have sufficient sample power to detect small but clinically relevant improvement in mortality. Early trials of PE thrombolysis (29, 30), though of historical interest, have limited relevance in the era of modern thrombolytic therapies, as our agents and our understanding of risk factors and management of complications have evolved. In the absence of sufficiently powered randomized controlled trials, discussions of thrombolysis for PE have focused on surrogate markers presumed to be important in determining mortality. Specifically, improvement in oxygen requirements, V/Q scans, pulmonary angiograms, pulmonary artery pressure, right ventricular function, and decreased recurrent PEs have served as markers of therapeutic "efficacy." A recent trial (33) evaluated 719 hemodynamically stable PE patients with right ventricular dysfunction and reported a 30-day mortality of 11.1% in the heparin group versus 4.7% in the thrombolytic group ($p<0.018$). There was a PE recurrence rate of 7.7% versus 18.7% in favor of the thrombolytic group ($p<0.001$). These benefits must be counterbalanced by the inherent risks of thrombolysis to determine the ultimate clinical "effectiveness."

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*Urokinase is presently unavailable for clinical use.

Massive PE with cardiogenic shock and hypotension, as in the patient presented here, has a mortality approaching 100% (34). The risk-benefit ratio in this patient group clearly favors thrombolytic intervention. A study comparing heparin alone versus heparin plus thrombolysis with streptokinase in PE patients with cardiogenic shock clearly favored thrombolysis (34). In hemodynamically stable patients, the indications for thrombolysis are controversial. Italian investigators (35) reported the results of 36 patients with angiographically proven PE who were randomized to receive either recombinant human-tissue-type plasminogen activator (rt-PA) or heparin alone. They document angiographic clot lysis and a decrease in pulmonary artery pressure, but obvious net clinical benefit. Goldhaber (36) demonstrated similar hemodynamic and angiographic improvement with a 57% increase in pulmonary perfusion and dramatic improvement in right ventricular function. This work motivated a relatively large, randomized, multicenter trial carried out at 13 American centers (24). This trial examined 101 hemodynamically stable patients who were randomized to receive rt-PA and heparin versus heparin alone. Baseline and follow-up echocardiograms were evaluated. No difference in mortality was noted. However, this study was only capable of demonstrating mortality benefits of greater than 15 – 20%; lesser reductions would not have been detected. Four-fifths of the enrolled patients were diagnosed by perfusion scans, one-fifth by angiography, dispelling the myth that angiograms are required before thrombolysis. Therapy with rt-PA followed by heparin provided striking improvement in right ventricular function and pulmonary perfusion compared with heparin alone (Table 4). With regard to right ventricular function, 39% of the rt-PA group improved and 2% worsened, compared to the heparin group, where only 17% improved and 17% worsened ($p<0.005$). Notably, no clinical episodes of recurrent PE occurred among rt-PA patients, but there were five (two of them fatal) clinically suspected recurrent PEs within 14 days in the heparin alone group ($p<0.06$). All five patients with recurrent PE had echocardiographic evidence of right ventricular hypokinesis. Goldhaber suggests that right ventricular hypokinesis predisposes to *in situ* thrombosis within the right ventricle, right atrium and caval system secondary to vascular congestion. Right ventricular hypokinesis may be a marker for larger peripheral clot burden, worse arterial oxygenation and a downward spiraling hemodynamic state. Whatever the mechanism, the finding of right ventricular hypokinesis clearly defines patients at high risk for clinical decline; these patients deserve consideration for thrombolytic therapy.

A Practical Approach

The figure outlines a diagnostic-therapeutic algorithm that is useful when considering an acutely ill patient with probable PE. Generally, confirmation of any diagnosis should

TABLE 4

Effects of TPA on Right Ventricular Function and Pulmonary Perfusion.

Right Ventricular Function	Worse	Improved	No Change
Heparin	17%*	17%*	66%
TPA	2%*	39%*	59%
Pulmonary Perfusion		Improved	
Heparin		1.5%	
TPA		14.6% **	

(*p<0.005, **p<0.0001)

Data from Goldhaber SZ, Haire WD, Feldstein ML, et al., modified with permission (24).

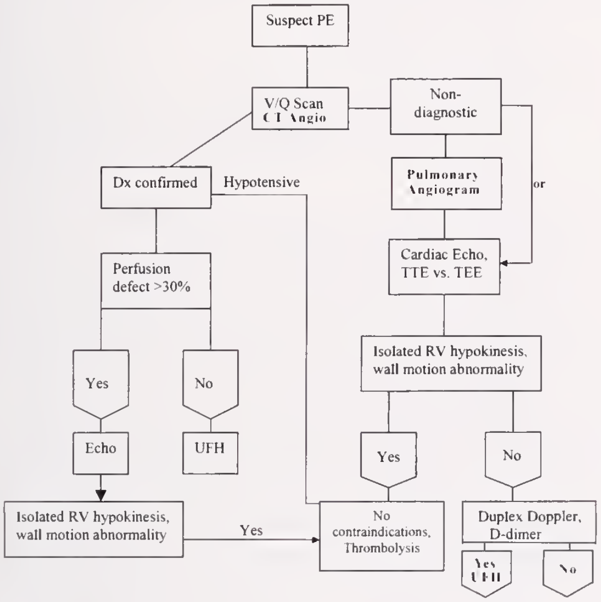

Figure. Strategy for evaluation of patients with pulmonary embolism for thrombolytic therapy. Echo = echocardiogram; RV = right ventricle; TTE = transthoracic echocardiogram; TEE = transesophageal echocardiogram; UFH = unfractionated heparin; V/Q scan = ventilation/perfusion scan (see text).

be encouraged. In hemodynamically stable patients, V/Q scanning can establish a diagnosis in about 25% of the patients who are ultimately confirmed to have a PE. CT angiography, which is less definitive with respect to quantifying the extent of any perfusion defect, also can be diagnostic in many patients. If the V/Q scan indicates a perfusion deficit greater than 30%, an echocardiogram should be done. A fraction of these patients will exhibit right ventricular dysfunction, and they will be at high risk for failure of standard heparin therapy. For this group of patients, the additional use of thrombolysis therapy should be considered.

Non-diagnostic V/Q scans remain problematic. Pulmonary angiography may be helpful in confirming the diagnosis in these patients. Stein et al. (37) maintain that invasive procedures such as pulmonary angiography in patients destined to receive thrombolytic therapy carry a significant risk of complications and that the risk of bleeding following thrombolytic therapy in patients with intermediate probability scans and high clinical suspicion (a high prevalence cohort) was less than the risks associated with pulmonary angiography. This study must be interpreted with caution, because it is a retrospective, population-based analysis of pooled data from PE and myocardial infarction patients. Finally, pulmonary angiography, though diagnostic, is difficult in "sick" patients and raises the complication rate of subsequent thrombolysis (37). In patients "too sick" to make a "definitive" diagnosis by pulmonary angiography, an echocardiogram may help to demonstrate acute right ventricular failure. With a high-risk patient for whom there is a strong clinical suspicion of PE, this documentation may be sufficient to proceed with thrombolytic therapy if there are no contraindications to thrombolysis. Contraindications are both absolute and relative. Evidence of active gastrointestinal bleeding, severe and uncontrolled hypertension, intracranial or intraspinal disease, recent (7 – 10 days) major surgery, and known bleeding diathesis are generally considered absolute contraindications. Other, more relative contraindications include a history of recent blunt or minor surgical trauma, advanced age, evidence for retinopathy, and drug allergy. However, our patient illustrates that even with those absolute "contraindications," in special life-threatening situations thrombolysis is indicated. If the echocardiogram fails to show right ventricular hypokinesis, then a duplex Doppler and D-dimer test may help to establish the diagnosis of PE and thereby support proceeding with heparin therapy. If these latter tests are non-diagnostic, then a decision to initiate anticoagulation must be made on clinical grounds.

Summary

Pulmonary embolism continues to result in excessive morbidity and mortality, particularly in the postoperative period. Identification of risk factors and appropriate DVT-PE prophylaxis based on risk stratification significantly reduce this morbidity and mortality. Life-threatening pulmonary embolism requires immediate recognition, heparin anticoagulation and consideration for thrombolytic therapy. Thrombolytic therapy offers hemodynamic improvement and improved gas exchange secondary to improvement in V/Q (reperfusion), and perhaps lowers the risk for recurrent pulmonary embolism and death. Definitive data demonstrating effectiveness awaits a large multicenter trial requiring more than 1,000 patients (to detect a 5% mortality benefit, assuming a 30% case fatality rate). Difficulty in rapidly and accurately attaining a diagnosis for acutely ill patients has limited the more general use of thrombolytic therapy. Two-dimensional echocardiograph offers accurate, valuable diagnostic information, identifies apparently hemodynamically stable patients at risk for recurrent pulmonary embolism and adverse clinical outcomes, and can be used to direct clinical decision making.

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Moses Presages Kubler-Ross:

Five Stages in Accepting Death, as Seen in the Midrash

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Abstract

This paper elucidates and explains an ancient midrash (rabbinic interpretation of a biblical text) through the lens of modern psychological theory. The midrash describes Moses' reactions to his approaching death. The paper points out that these reactions anticipate the five classic stages, described by Elizabeth Kubler-Ross, of coming to accept terminal illness: denial, anger, bargaining, depression and acceptance. The article shows the ancient rabbis' sensitivity to human feeling and the universal nature of human reaction through the dialogue and reactions they attribute to Moses. Finally, it shows how using this midrash offers a constructive model for approaching death, for Jewish and non-Jewish patients alike, as well as their caregivers.

Key Words: Thanatology, death, midrash, Kubler-Ross, pastoral care, acceptance.

Introduction

Thanatology, the study of death and dying, was for many years an outsider to the host of medical specialties. Perhaps because physicians and other caregivers try so hard to preserve life, it is difficult for them to admit to themselves, to patients, and to patients' families, that there will on occasion be no possible heroic intervention, no solution, no cure.

Yet patients may be able to add dignity and meaning to their death if they are afforded the opportunity, when possible, to acknowledge that they are dying. Through honest evaluation and communication, medical professionals can, in certain situations, facilitate a "good death."

Of course, some patients will never accept the reality of death, despite caring, professional support and guidance. However, with patience and attention to the mental and emotional work involved, much can be accomplished.

I [Dr. Knight] recently visited a patient of mine who was dying in the Palliative Care Unit (PCU) of the Royal Victoria Hospital. On most of those visits, I saw a man of about fifty-five sitting in the family room. We eventually began to talk. His father, a man of eighty-five, was dying of a malignancy. I asked the son why he was there so often. He replied that his father had always supported his successes at school, had been proud of his athletic achievements, and had praised him for his work in the family business. He added, "But I was hoping that before he died, he would tell me that he loved me."

Several weeks later I saw the son offering gifts to the PCU nurses. He informed me that his father had died, and he said, "I think that before he died, he told me that he loved me." Only because the father knew his time was limited could he work on saying the things he had left unsaid. Only because the son knew his father was dying could he create opportunities to hear them.

Dr. Elizabeth Kubler-Ross was a pioneer in the field of palliative care, active preparation for death without medical intervention. Through clinical observation, she perceived that terminal patients usually experience a similar range of emotions and responses: denial, anger, bargaining, depression and acceptance (1).

These stages are descriptive, not prescriptive, meaning that caregivers should seek to listen and affirm the patient's emotions, when and if they surface, rather than try to move the patient along a set path or timetable. They may find that stages two, three and four appear in a different order, as in the midrash we will describe, or that a stage is skipped altogether. Still, an overall awareness of the general pattern can help families and caregivers assist the dying patient.

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This paper analyzes a midrash, a rabbinic elaboration on a biblical story. This midrash, which probably dates from the middle of the first millennium of the Common Era (C.E.), portrays Moses' response to the news of his impending death. He experiences the five stages identified by Kubler-Ross. Significantly, for physicians, it is only because God informs him of his impending death that Moses has the opportunity to move through the stages of resistance, to the point where he can die peacefully. The analysis of the midrash points out how the stages Kubler-Ross identified may be rooted in a timeless human experience. In addition, it may convince medical personnel of the important work that can be done in the months, weeks or days preceding death if they do not try to shield the facts from the patient, and if the patient is permitted or even encouraged to express openly the various feelings that arise.

The Five Stages in More Detail

1. Denial. Denial acts as a buffer from the shocking news and is usually a temporary defense. It includes thoughts like "it can't be true" and "this can't be happening to me," and actions such as blaming an erroneous pathology report or mixed-up x-ray, and seeking a second opinion.

2. Anger. When denial is not maintained, it gives way to anger and resentment — responses to perceived unfairness or injury — which are often directed at family and at physicians, either in their own capacity, or as representatives of God.

3. Bargaining. This approach may be helpful to the patient in the short term. It usually consists of an agreement to accept the inevitable, but at a later date, to postpone the decree, as it were. Most patients, even those who do not have a formal religious affiliation, make their bargains with God, who is seen as having the power over life and death.

4. Depression. When the terminally ill patient can no longer deny the illness, resistance and rage will give way to a sense of great loss. Symptoms may include withdrawal into silence or limitation of human contact. Kubler-Ross calls this a preparatory depression. Perhaps the patient is preparing for the ultimate isolation. The first four stages can vary in length and intensity from patient to patient.

5. Acceptance. With enough time and help, the patient exhausts his or her anger and depression, and arrives at the stage of acceptance. Through expressing feelings and "tying up loose ends" with family, business and personal life, the patient who reaches this stage is able to discuss death with calmness and equanimity. This stage is not just a wish to end pain and suffering, but a genuine acceptance of reality.

The Midrash

Midrash is homiletical rabbinic commentary on the Hebrew Bible, often responding to perceived redundancy, inconsistency or a curious turn of phrase in the text. In addition to their ostensible goal of elucidating the biblical text, early preachers of midrash sought to teach lessons of contemporary relevance. At some point, the oral interpretations became codified according to the order of the Bible. "Midrash" (plural "midrashim") refers to the individual nugget of commentary as well as each edited volume, and also the entire genre. While it is difficult to date individual midrashim, collected works of midrashim were completed as early as 400 C.E., with the bulk of them being edited during the period 600 – 900 C.E., and some later collections in the early Middle Ages (2). This particular midrash, which presumably had meaning for congregations or audiences at the time of its composition, also addresses dilemmas which still face us today.

This midrash is long, so I will just refer to the relevant parts, but the text can be found in full in the Hebrew in Midrash Rabbah, Parashat VeZot HaBracha, 11:10, and in English translation in *The Book of Legends*, ed. HN Bialik, YH Ravinitzky; transl. WG Braude; New York: Schocken Books; 1992. pp. 101 – 105. It comments on the Biblical verses Deuteronomy 31:14: "The Lord said to Moses: the time is drawing near for you to die ..." and Deuteronomy 34:1 – 8:

> Moses went up from the steppes of Moav to Mount Nevo, to the summit of Pisgah, opposite Jericho, and the Lord showed him the whole land: Gilead as far as Dan; all Naphtali; the land of Ephraim and Menasseh, the whole land of Judah as far as the Western Sea; the Negev and the Plain — the Valley of Jericho, the city of palm trees — as far as Zoar. And the Lord said to him, 'This is the land of which I swore to Abraham, Isaac and Jacob: I will assign it to your offspring. I have let you see it with your own eyes, but you shall not cross there.'

> So Moses the servant of the Lord died there, in the land of Moav, at the command of the Lord. He buried him in the valley in the land of Moav, near Bet-Peor; and no one knows his burial place to this day. Moses was a hundred and twenty years old when he died; his eyes were undimmed and his vigor unabated. And the Israelites bewailed Moses in the steppes of Moav for thirty days.

At the point where the midrash begins, Moses has had a long and fruitful, though difficult life. "Moses was a hundred and twenty years old when he died; his eyes were undimmed and his vigor unabated." He is not yet ready to die. When God informs him that he will not merit entering the land of Israel, which he has labored so long to reach, Moses' first response is denial. (Most likely, Moses understands that God is telling him, in a gentle, indirect manner, that he will die. A second possibility is that not entering the land of Israel is tantamount to death for Moses.) The midrash tells us:

> The High Court revealed itself to him and declared, 'It is my decree that you should not pass over,' [as it is said], '*For you shall not go over the Jordan*' (Deuteronomy 3:27). Moses, however, made light of this, saying, 'Israel have many times committed great sins, and whenever I prayed for them, God immediately answered my prayer ... (Exodus 32:24, Numbers 14:12). Seeing then that I have not sinned from my youth, does it not stand to reason that when I pray on my own behalf God should answer my prayer?'

Moses is unwilling to believe that the decree is true. He continues acting with confidence and cool nerve. However, this stage does not last permanently. As Moses realizes that the forces ranged against him are too powerful for him to ignore, he enters a stage of inwardness and withdrawal:

> When, however, Moses saw that the decree against him had been sealed, he took a resolve to fast, and drew a small circle and stood therein, and exclaimed, 'I will not move from here until Thou annullest that decree.'

Kubler-Ross would call this stage depression. The fasting symbolizes great sorrow, and the drawing of the circle, which elsewhere in Jewish sources (3) is a way of protesting and persuading God to reverse a negative decree, here seems to represent Moses' cutting himself off from other people and sitting for days in isolation.

From depression, Moses moves immediately into anger. He cries out to God about the unfairness of the decree:

> 'Is this the reward for the forty years' labor that I went through in order that [Israel] should become a holy and faithful people ...?'

After this outburst, Moses' resolve is weakened, but he still does not want to give in. With only one hour left, according to the midrash, the stage of bargaining begins. Here we cite only Moses' side of the dialogue, though the midrash includes God's responses as well:

> Whereupon Moses said to God, 'Master of the Universe, if Thou wilt not bring me into *Eretz Israel* [the Land of Israel], leave me in the world so that I may live and not die'... Said Moses to God, 'Master of the Universe, if Thou wilt not bring me into *Eretz Israel* ... let me become like the beasts of the field that eat grass and drink water and live and enjoy the world... Master of the Universe, if not, let me become in this world like the bird that flies about in every direction and gathers its food daily and returns to its nest toward evening; let my soul likewise become like one of them.'

The responses of God are omitted here so as to highlight the arguments brought forward by Moses, exhibiting his desperate efforts to avoid death. He is willing to give up almost anything, including his very humanity, in order to avoid death. The willingness to sacrifice in return for a compromise, along with the continuing arguments, "lowering the ante" each time, clearly identify this behavior of Moses with the stage of bargaining.

This stage can last any length of time, but Moses does not have much time. Fortunately, due largely to the gentle care and support of his caregiver, in this instance God, Moses is able to reach a gradual acceptance of the decree.

> Sammael, the wicked angel, the chief of all the accusing angels, was awaiting the death of Moses every hour, saying, 'When will the time or the moment arrive for Moses to die,

> so that I may descend and take away his soul from him?'

Moses is not willing to surrender his soul to Sammael, but when God Himself offers to attend to Moses, the servant of God begins to accept his imminent death. This section of the midrash is based on the biblical verse "So Moses the servant of the Lord died there, in the land of Moav, at the command of the Lord. *He* buried him in the valley in the land of Moav, near Bet-Peor; and no one knows his burial place to this day" (4). The verse states explicitly that *God* buried Moses and reiterates that no human was there (according to other traditional interpretations of the text, God arranged this situation so that the burial site of Moses would not become a site of undue attention and worship). Here our midrash continues:

> Said Moses to God, 'Master of the Universe, remember the day when Thou didst reveal Thyself unto me in the bush ... remember the time when I abode on Mount Sinai for forty days and forty nights ... I implore Thee, do not hand me over into the hand of the Angel of Death.' Thereupon a Heavenly voice was heard saying to him, 'Fear not, I myself will attend to you and your burial.'
>
> At that hour, Moses arose and sanctified himself like the Seraphim [angels], and God came down from the highest heavens to take away the soul of Moses, and with Him were three ministering angels, Michael, Gabriel and Zagzagel. Michael laid out his bier, Gabriel spread out a fine linen cloth at his bolster, Zagzagel one at his feet. Michael stood at one side and Gabriel at the other side. God said, 'Moses, fold your eyelids over your eyes,' and he did so. He then said, 'Place your hands upon your breast,' and he did so. He then said, 'Put your feet next to one another,' and he did so.

In this section we see Moses coming to an acceptance of his death. As the angels initiate several of the Jewish rituals which honor the deceased — wrapping the body in white linens, having it attended until the funeral by guardians (*shomrim*) — Moses himself begins to take an active role in preparing for death. As he purifies himself, perhaps with water, which is part of the pre-funeral ritual of washing or *taharah*, as he closes his eyes and as he assumes the position of eternal rest, Moses is literally exhibiting his willingness to accept death.

Discussion

On one level, the midrash fills in the blanks left by the biblical story of Moses' death — How did he react when he heard the news? Who actually buried him if no one knew of his place of burial? Did he resent not being able to enter the land of Israel after he had led his people so devotedly for forty years? More important, however, the midrash shows that the sage(s) who composed it were in touch with human nature, and that human nature has not changed much in 1500 years.

Although their understanding of human reactions to mortality was probably intuitive (or perhaps inspired) rather than scientific, the rabbis of the midrash sensed that each of the reactions which Elizabeth Kubler-Ross later formalized into five stages is natural and helpful in its own way. However, just as experience suggests that the order and relative length of each one may vary from case to case, stages 2, 3, and 4 are manifested in a different order in the midrash than in Kubler-Ross' research. (Perhaps the humble Moses was more likely to turn inward, examining his own actions, before blaming God. Thus fasting, symbolizing contrition and depression, precedes anger in the midrash.) Indeed, Kubler-Ross conceded that these stages may not occur in the same order and in the same manner for everyone. However, the essence of a path through different emotions still applies. The inherent goal of this ancient process, seemingly God-given, is an exhaustion of the possibilities and a gradual reconciliation. If the patient has not been able to express and thereby exhaust the stages of anger or bargaining, they will resurface and interfere with the attainment of final peace.

The account of Moses' journey toward accepting his inevitable death points to several elements which can be of guidance to patients as well as to caregivers who are trying to help their patients come to terms with death. It is important to be aware that most patients experience most of the stages, for varying lengths of time. To express these feelings, patients will often initiate conversation, but it is the responsibility of caregivers not to block this line of communication. By legitimizing and listening to all of the patient's reflections, be they angry, somber or morose, a caregiver or family member can be of great help. Setting aside one's own discomfort with death can help the patient work through feelings that may eventually bring a sense of peace and acceptance.

Anger may be especially disconcerting, but it is an integral part of the process. Moses enjoyed a close relationship with God and felt that he could communicate with God directly. Since God was the perceived source of the decree and since Moses had conversed with God over a lifetime of prayer, Moses could direct his anger at the source of his grief. If a patient perceives God as the source of illness, based on theology or emotion, the patient may well be angry at God. A lifetime of communication with God is a good basis for honest expression of anger at this point. For those who feel uncomfortable expressing anger with God or who assume that their tradition discourages such feelings, reading a psalm (5) may be a good starting point. Alternatively, the psalms may allow a very devoted person who has not realized that one is permitted to be angry at God, to express these feelings; if the psalmist could do it, the patient may realize, then surely it is permitted within the Jewish and Christian traditions.

Most important, perhaps, the responses of Moses in the midrash can give an authentically Jewish model to a patient who wishes to approach death with equanimity but has been trained to fight it till the end.

Moses was at first highly resistant to dying. If generalizations can be made, Jewish patients tend to fight against death even past the point when other patients may say, "It is in God's hands." "Central to Jewish culture is a passion for life, which can prove difficult in the palliative care setting ... Despite the fact that the 'good death' has strong biblical antecedents, it is not what is normally emphasized" (6). More familiar in a Jewish setting is the sanctity of life, the duty to preserve life, and a predominantly positive attitude toward healing.

Death is especially unwelcome to Jews, who do not share the Christian view of death, namely that "it is inevitable and not to be feared but to be accepted as the closing out of one form of being in hope of another, an eternal existence with God" (7). While there are Jewish visions of an afterlife, they are not so immediate or so central as is the Christian concept of "being with Jesus now." It is significant that, according to the midrash, even Moses, who was so attuned to God's wishes and plans, felt comfortable crying out to preserve his life and lengthen his days, despite God's decree to the contrary.

On the other hand, if Moses could come to a gradual acceptance of his mortality, even though he still had the will to see and accomplish many more things, perhaps reconciliation to this fate is not something beyond the patient's reach; certainly it is an approach condoned by Jewish tradition, as expressed by the dramatic dialogue of the midrash.

Finally, we learn from the midrash how great an honor it can be to attend someone in their last hours of life, and what a difference a calm, loving presence can make to the dying person. God's presence in the midrash ultimately allays Moses' fears and enables him to confront death. Of course, there is a time for medical intervention and treatment, but when the end really comes, it is the time for peace. Our most sacred mission as human beings is to imitate God's attributes of love, compassion and giving.

The midrash concludes, "Thereupon God kissed Moses and took away his soul with a kiss of the mouth, and God, if one might say so, wept ..."

Conclusion

It is frightening and painful to be in the presence of terminal illness. However, if physicians and caregivers can help release the emotional blockages — letting the patient guide the conversation, experience each stage to its fullest, and ultimately attain a more peaceful death — they need not fear their inability to make any further medical contributions toward prolonging life. The emotional and spiritual contributions of listening to the patient's deepest thoughts when others are simply trying to cheer him up, can be extremely valuable in their own right. Most important, shielding the patient from the true nature of the disease can rob that person of the opportunity to have this kind of closure. Some deaths occur without warning; when the patient does have the opportunity and the mental capacities to come to terms with approaching death, physicians should err on the side of reality rather than protecting the patient from bad news. Though this approach, to encourage the patient to overcome the illness, can have beneficial effects at early stages of disease, its well-meaning value dissipates when death becomes inevitable and imminent. If the father in the case cited in the introduction had not been sure he was going to die, he probably could never have mustered the courage to tell his son, "I love you."

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3. For example, in the exploits of Honi the circle drawer in the Babylonian Talmud, Tractate Ta'anit, 23a.
4. Deuteronomy 34:5 – 6.
5. Psalms 10, 22 express anger and 5, 6, 16, 17 express anger coupled with a plea for attention: "Hearken to the sound of my outcry, my Lord …"; "attend to my entreaty, give ear to my prayer." The "enemies" in Psalms 3 and 5 can be interpreted as the illness; thus, by reading these psalms the patient can enlist God's help to gain power to fight the illness.
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Bronchiolitis Obliterans in a Patient with Ulcerative Colitis Receiving Mesalamine

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Abstract

An 18-year-old woman with ulcerative colitis (UC) developed diffuse pulmonary infiltrates and hypoxemia three months after reinstitution of oral mesalamine. Lung biopsy revealed bronchiolitis obliterans with interstitial pneumonitis. Clinical and radiographic abnormalities improved upon discontinuation of mesalamine and treatment with corticosteroids. This patient presented the problem of differential diagnosis of pulmonary disease associated with inflammatory bowel disease (IBD), including lesions believed to result from lung involvement secondary to IBD, as well as adverse reactions to medications. We present and analyze evidence associating mesalamine with pulmonary toxicity in this patient, but emphasize that the distinction between adverse drug reaction and extraintestinal manifestations of IBD is difficult.

Key Words: Bronchiolitis obliterans, ulcerative colitis, mesalamine.

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic diseases of the gastrointestinal tract and comprise the inflammatory bowel disease (IBD) complex. They involve extraintestinal sites, including the lungs, in up to 25% of patients (1). Though uncommon, several patterns of pulmonary involvement due to treatment of IBD with sulfasalazine, methotrexate and azathioprine have been reported. Similar inflammatory lesions have been described in patients receiving mesalamine preparations (aminosalicylate, 5-ASA) (2–4). The following is a report of a patient with UC who developed bilateral diffuse pneumonitis shortly after reinstitution of oral mesalamine (Asacol®— Proctor and Gamble, Cincinnati, OH) and thus presented a difficult differential diagnostic problem.

Case Report

An 18-year-old nonsmoking woman was well until December 1990, when a diagnosis of UC was established. Treatment with intravenous corticosteroids, oral sulfasalazine, and parenteral nutrition was initiated. She improved, and one month later medications were changed to oral mesalamine 1.6 g/day and 5-ASA enemas 4 g/day. Oral 6-mercaptopurine (6-MP) 50 mg/day was added because of persistent bowel symptoms and colonic inflammation. Complete remission was achieved in February 1993, and by August 1993 all medications were withdrawn. The subsequent clinical course is summarized in the Table. In November 1994, recurrence of colitis necessitated reinstitution of therapy with mesalamine, oral 6-MP and 5-ASA enemas. Two months later, dyspnea on exertion, nonproductive cough, pleuritic chest pain and intermittent temperature to 39°C developed and worsened despite antibiotic treatment. She was admitted to a local hospital with severe dyspnea in March 1995. Manifestations of UC had improved. Physical examination revealed a respiratory rate of 30/min,

TABLE
Time Course of Patient's Condition.

Date	Status	Action taken
11/94	Active colitis	Mesalamine prescribed
1/95	Fever and dyspnea	
3/95	Hospitalization	
	Abnormal chest x-ray	Stopped mesalamine
5/1/95	Open lung biopsy	Corticosteroids prescribed
5/7/95	Improvement	Tapered steroid
6/1/95	Chest x-ray normal	Resumed activities

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temperature 37.1°C, bronchial breath sounds at both lung bases and moderate abdominal tenderness. The remainder of the examination was normal. Laboratory findings revealed a white cell count of 27,000/mm^3 with 88% neutrophils, 4% band forms, 5% lymphocytes, 2% monocytes and 1% eosinophils. Arterial blood gas revealed P_{aO2} of 65 mm Hg and P_{aCO2} of 41 mm Hg while the patient was receiving nasal oxygen at 5 L/min. Chest radiography showed diffuse, patchy, peripheral densities with focal areas of consolidation involving the left lung, thickening of left pleura and lesser densities on the right (Fig. 1). A previous chest radiograph performed in 1991 was normal. Treatment with intravenous broad-spectrum antibiotics was initiated. Mesalamine, oral 6-MP and 5-ASA enemas were discontinued. Examination with fiberoptic bronchoscopy revealed only minimal bronchial inflammation. Severe hypoxemia precluded transbronchial biopsy. Microscopic examination of bronchoalveolar lavage fluid was negative for pathogens. Upon transfer to the Mount Sinai Medical Center, New York, the patient received video-assisted thoracoscopy. Biopsy of the left lower lobe was performed.

On gross examination, the pleura appeared diffusely inflamed and thickened, a moderate pleural effusion was present and the involved lung was consolidated. The microscopic examination of the biopsy of lung tissue was remarkable for two main findings: (a) One of the sections revealed an area of capillaritis, a lesion characterized by the presence of numerous neutrophiles in the alveolar spaces with hemorrhage and nuclear "dust" fragments (karyorrhexis) (Fig. 2. A). Pulmonary capillaritis has histologic similarity to systemic leukocytoclastic vasculitis, frequently associated with hypersensitivity to medications, although the pulmonary equivalent seen here can also be the expression of complex and poorly understood diseases (Wegener's granulomatosis, Goodpasture syndrome, systemic lupus erythematosus [SLE]). (b) Numerous bronchioles showed intraluminal plugs of granulation tissue ("bronchiolitis obliterans") (Fig. 2. B). Our micrograph(s) revealed progressive thinning of the ciliated respiratory epithelium leading to an epithelial ulceration, from which the connective tissue polyp emerges to fill the bronchiolar lumen. In this case, the number of such bronchiolar obliterative lesions was impressive, as was the

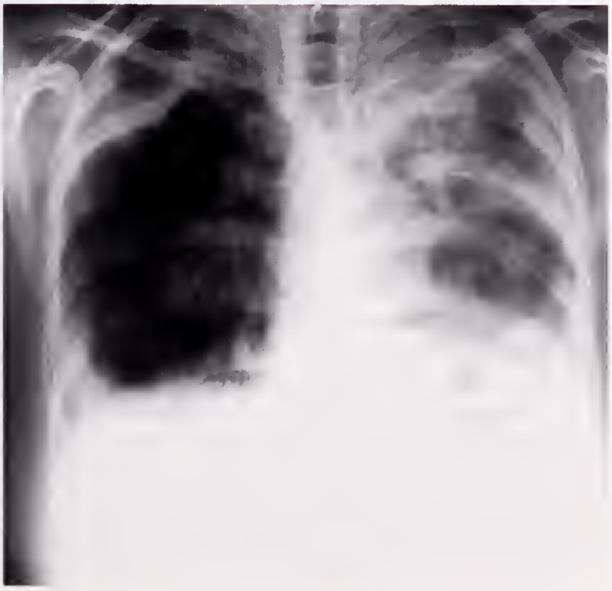

Fig. 1. Admission chest PA showing diffuse pleuroparenchymal involvement of both lungs, left lung worse than the right.

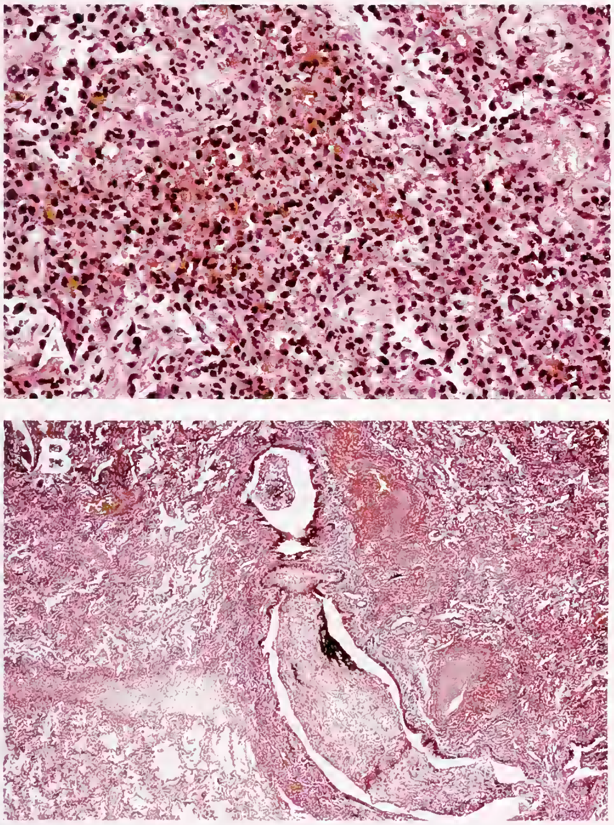

Fig. 2. **A**. Lung parenchyma with capillaritis. Note the accumulation of neutrophiles tracking the alveolar wall. Alveolar spaces are filled with macrophages and erythrocytes. Chromatin fragments ("nuclear dust") also are seen. **B**. Lung parenchyma with bronchioli. Note the polyp of young connective tissue in the lumen. This rises from an area of epithelial ulceration that appears following epithelial attenuation.

paucity of the organizing pneumonia representing the alveolar equivalent. In fact, this alveolar equivalent ("organizing pneumonia"), which is usually seen in bronchiolitis obliterans with organizing pneumonia (BOOP), is seen more frequently than the bronchiolar component. The bronchiolar walls, as well as many alveolar walls, revealed chronic inflammation. Bronchiolitis obliterans has been associated with multiple idiopathic conditions, drug reactions and postinfectious syndromes. Cultures of pleural fluid and lung tissue showed no evidence of bacteria, fungi or acid-fast organisms.

Treatment was initiated with intravenous methylprednisolone, 40 mg every six hours. The patient improved during the next four days, with an increase in oxygen saturation and partial clearing of infiltrates (Fig. 3). Corticosteroids were tapered to oral prednisone 40 mg once per day. Within three weeks, she was engaging in most physical activities and her chest radiograph revealed almost complete clearing of all radiographic infiltrates. Symptoms of colitis were minimal and 6-MP was restarted without recurrence of pulmonary disease.

Discussion

The patient demonstrates the difficulty in establishing the etiology of pulmonary disease complicating IBD. Oral mesalamine, 6-MP and 5-ASA enemas were prescribed for a relapse of bowel disease. While intestinal symptoms improved, fever and diffuse pneumonitis developed. She improved with corticosteroid therapy. The clinical course and lung histology strongly suggest a drug-induced pulmonary inflammatory process, most likely due to mesalamine. However, pulmonary involvement as an extraintestinal manifestation of IBD cannot be ruled out.

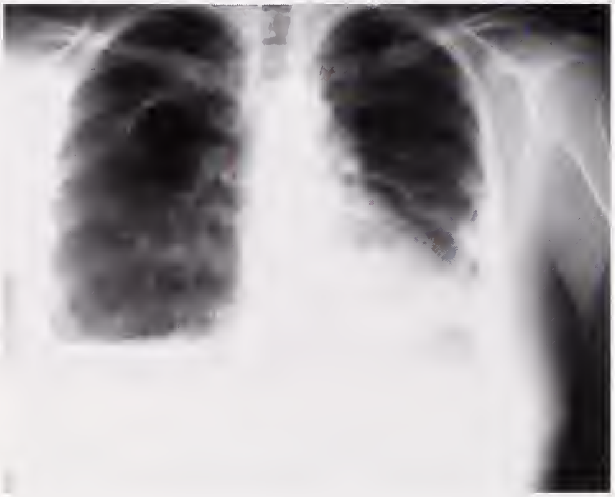

Fig. 3. Chest PA four days after discontinuing mesalamine and adding prednisone, showing improvement with remaining patchy consolidation of the left lower lobe and lingula, pleural thickening and lesser involvement of the right lung.

A variety of pulmonary disorders in patients with IBD have been reported. Rarely, biopsy of the lung in patients with IBD has revealed epithelioid granulomas with multinucleated giant cells morphologically similar to findings seen on intestinal biopsy (5–7). Camus et al. (8) studied 33 patients with IBD and pulmonary disorders (27 with UC and 6 with CD). Four clinicopathologic patterns were encountered: (a) airway disease, including tracheal obstruction, chronic bronchitis, bronchial suppuration, and bronchiectasis; (b) interstitial lung disease, including BOOP and the syndrome of pulmonary infiltrates and eosinophilia (PIE); (c) serositis; and (d) necrotic parenchymal nodules. Pulmonary manifestations began an average of 9 years after the onset of bowel disease and only 11% of patients had active bowel disease when pulmonary symptoms arose. Other extraintestinal involvement was present in two-thirds of patients. Only one-third of patients were receiving medications for IBD when they developed pulmonary disease. The most frequently occurring pattern of pulmonary involvement was airway disease. In Camus' series and in other reports of pulmonary disease in IBD (9, 10), it seems unlikely that the lung disease was drug-induced, since most patients were not receiving medications. Spira et al. have confirmed the prominence of airway disease in 7 patients with IBD, reporting bronchiectasis in 5 and chronic bronchitis in 2 of their patients (11). Levine and Lukawski-Trubish have postulated that the similarity of the gastrointestinal and lung mucosal immune systems is responsible for the occurrence of bronchial disease in patients with IBD (12).

While clinically apparent pulmonary disease complicating IBD is rare, subclinical pulmonary abnormalities may be relatively common (13–16). Heatley et al. (13) reported reduction in diffusing capacity for carbon monoxide (DLCO) in 25% of patients with IBD and spirometric abnormalities consisting of obstruction and restriction in 50% of 102 patients. Bonniere el al. (14) demonstrated alveolar lymphocytosis in bronchoalveolar lavage fluid of at least 18% in 12 of 22 patients with CD who had no pulmonary symptoms or chest radiographic abnormalities. Pulmonary function abnormalities, most commonly reduced DLCO, were present in 52%. Ussov et al. (17) demonstrated increased lung uptake of ^{111}Indium-labeled polymorphonuclear cells, indicative of abnormal margination, in patients with IBD without clinically apparent lung disease. Adenis et al. (18), using clearance of inhaled ^{99m}Technetium diethylenetriaminepintaacetic acid (DTPA), reported that patients with Crohn's disease may have increased pulmonary vascular permeability due to latent alveolitis.

Several medications prescribed for treatment of IBD have been associated with adverse pulmonary reactions. Sulfasalazine, which consists of 5-ASA and sulfapyridine linked by an azobond, may cause fever, rash, arthralgia and hemolytic anemia (19, 20). Rare pulmonary adverse reactions, characterized by cough, dyspnea and bilateral patchy lung infiltrates with or without peripheral eosinophilia are believed to represent a hypersensitivity reaction to the sulfapyridine moiety (21–23). Histopathologic findings have included progressive interstitial fibrosis, interstitial pneumonitis without fibrosis (24) and bronchiolitis obliterans (8, 25, 26). Improvement has been demonstrated upon discontinuation, and recurrence upon rechallenge with sulfasalazine (27). Methotrexate and azathioprine (28) may also induce pneumonitis. Cases of lung toxicity due to 6-MP are extremely rare (29). Mesalamine is a newer preparation of 5-ASA, available in oral and rectal forms, which does not contain sulfonamide. Though the incidence of side effects is significantly lower than with sulfasalazine, urticarial rash, headache, interstitial nephritis, myocarditis, pericarditis and pancreatitis have been reported (30–34). Pulmonary abnormalities, including BOOP, have been reported in patients taking oral as well as rectal preparations of mesalamine. Reinoso et al. (2) described hypoxemia, bibasilar pulmonary infiltrates and diminished DLCO in a 64-year-old woman with UC who had been talking oral mesalamine for two years. Biopsy was not obtained, but the evidence of pulmonary disease diminished following discontinuation of mesalamine. Welte et al. (3) described interstitial lung infiltrates which developed 10 days after rectal mesalamine was initiated in a 67-year-old man with UC. BOOP was reported by Swinburn et al. in a 20-year-old woman taking oral mesalamine; clinical recovery followed treatment with corticosteroids (35). In Camus' series, lung biopsies from six patients revealed BOOP. Three of these patients were receiving preparations of mesalamine, 1 was receiving sulfasalazine and 2 were receiving no medications. Thus, several case reports have associated mesalamine with adverse pulmonary reactions, particularly bronchiolitis obliterans and BOOP.

The evidence suggests, but is not conclusive, that our patient's pulmonary disease was caused by mesalamine. Mesalamine has been associated with pulmonary disease, including BOOP, in at least 11 patients. Therefore, mesalamine-induced disease should be considered in the differential diagnosis of patients with IBD who develop pulmonary abnormalities. However, BOOP and bronchiolitis obliterans have been documented in patients with IBD not receiving medications (26) and resolution has occurred despite continuation of mesalamine (8). Thus, the distinction of an adverse drug reaction from pulmonary involvement by IBD itself remains a difficult challenge complicating the management of these patients. Corticosteroids have proven beneficial regardless of whether pulmonary disease is drug-induced or due to IBD. Therefore, in IBD patients with severe pulmonary disease, a trial of corticosteroids may be indicated provided an infectious etiology has been excluded. Alternatively, patients with milder disease can be managed by discontinuation of the suspected medication and observation.

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Can a Drug-Induced Pulmonary Hypersensitivity Reaction Be Dose-Dependent?

A Case with Mesalamine

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Abstract

Mesalamine-induced pulmonary adverse drug reactions (ADRs) in the course of therapy for inflammatory bowel diseases are rare events, having been reported in only 21 cases. This response, resembling hypersensitivity pneumonitis, is considered to be immunologically mediated and thus dose-independent. We report the case of a 70-year-old woman with ulcerative colitis (UC) who developed biopsy-proven interstitial pulmonary disease (lymphocytic alveolitis and mild interstitial pulmonary fibrosis) three months after starting mesalamine therapy.

The usual treatment in cases of ADR is cessation of the drug and initiation of corticosteroids. In this case, we continued the mesalamine therapy but halved the dose, and did not add corticosteroids. This approach led to a remission of the pulmonary manifestations without a resurgence of UC symptoms.

Based on a review of the literature and our own observation, we challenge the concept that mesalamine-induced pulmonary injury is always due to a hypersensitivity reaction. The evidence suggests that in some cases pulmonary ADR is dose-related; in such instances the most accepted therapy is not necessarily the most appropriate one.

Key Words: Mesalamine, ulcerative colitis, adverse drug reaction, pulmonary manifestations, hypersensitivity reaction.

Introduction

Sulfasalazine and 5-aminosalicylic acid (5-ASA or mesalamine) releasing preparations are commonly used to treat mild or moderately active ulcerative colitis (UC) and Crohn's disease (CD), and to maintain remission (1). However, up to 30% of patients taking 4 g/d of sulfasalazine develop adverse drug reactions (ADRs) (1). These reactions can be categorized as either plasma-concentration-dependent (i.e., they respond to a reduction of the dose), or plasma-concentration-independent (i.e., they do not so respond) (2). Symptoms of dose-dependent reaction include headaches, nausea and fatigue, whereas dose-independent reactions include rashes, hepatitis, nephritis and pneumonitis. The latter reactions are thought to be the manifestations of an allergy (or a hypersensitivity). The terms "drug hypersensitivity" and "drug allergy" are often used to describe the reactions mediated by the immune system (3).

In contrast, mesalamine, which lacks the sulfapyridine moiety considered responsible for most sulfasalazine ADRs, when taken up to 4.8 g/d, appears to induce no more dose-related reactions than does a placebo in a controlled study. Although such reports are infrequent, mesalamine is known to induce hypersensitivity reactions such as nephritis, pancreatitis and pneumonitis (1, 2). In the presence of a hypersensitivity reaction, it is recommended, by many, that the drug be discontinued and corticosteroids be administered (4, 5).

We present our experience with a patient with UC, who, during treatment with oral mesalamine, developed interstitial lung disease (ILD), weakly positive antinuclear antibodies (ANA) and a progressive increase in the value of the nonpancreatic fraction of amylasemia. Once the signs of pulmonary injury became manifest we treated the patient, who was by then in remission of the UC, in an unconventional way. We continued the mesalamine but halved the initial dose, from 2.4 g/d to 1.2 g/d, which was still above the minimum (0.8 g/d) effective maintenance dose suggested. (1, 6). We did not administer corticosteroids. Four years after we reduced the maintenance dose, the patient is still in remission, without any sign of ADR.

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We have reviewed the literature to assess whether an alternative exists to the widely accepted concept that mesalamine-induced pulmonary injury is the result of an immunological or idiosyncratic reaction. A survey of 21 cases showed that in two instances a rechallenge or a continuation of mesalamine therapy did not elicit a recurrence of ADRs, and in three other cases maintenance doses of corticosteroids failed to prevent ADRs. In addition, in about half of the cases, no treatment with corticosteroids showed comparable outcomes to cases in which corticosteroids were administered. Based on these findings, we propose that in some cases the ADRs might not be immunologically mediated, and a rethinking of the therapeutic approach in these special cases might be in order.

Case Report

A 70-year-old white woman, with a 10-cigarettes-per-day smoking habit, was admitted to the hospital with the following complaints: fever (38°C), abdominal pain and one week of diarrhea containing mucus and blood. She had no pulmonary complaints. Ten years earlier she had been diagnosed with autoimmune hypothyroidism, for which she was receiving therapy with L-thyroxine.

Results of some laboratory tests were as follows: erythrocyte sedimentation rate, 83 mm/hr; C-reactive protein, 9.23 mg/dL; and $\alpha 2$ globulin fraction, 15.2%. ANA and autoantibodies anti-DNA were negative. The chest radiograph was normal (Fig. A).

Colonoscopy revealed hyperemic mucosa with pseudopolyps and deep ulcerations extending to all colonic segments; multiple biopsies were consistent with UC (diffuse inflammatory infiltrates, crypt abscesses).

Therapy with prednisone (75 mg/d for 10 days and then gradually tapering off), coated mesalamine (Asacol®) at oral dosage of 2.4 g/d, and ranitidine 300 mg/d was instituted. The therapy resulted in a rapid resolution of symptoms. A colonoscopy performed 2 months later revealed no ulcerations. At this point the corticosteroids were discontinued, while the 5-ASA was maintained at the same dosage.

Three months after beginning the therapy, the patient started complaining of a dry cough and dyspnea on effort. There was no evidence of cardiac disease. Chest x-ray revealed diffuse accentuation of the pulmonary reticulum (Fig. B), and high-resolution computerized tomography (CT) evidenced small, diffuse opacities.

Laboratory results showed pH, P_{aO2}, P_{aCO2}, S_{aO2} (oxygen-saturation) and HCO_3 values in arterial blood of 7.46, 49 mm Hg, 39 mm Hg, 86%, and 28 mmol/L respectively. Also noted was the appearance of antinuclear antibodies (ANA) with homogeneous pattern (titre 1:40) and anti- DNA (titre 1:20). Other auto-antibodies, including the antineutrophil cytoplasmic antibodies (ANCA), were absent.

Pulmonary function tests showed a restrictive pattern. Bronchoscopy was negative and examination of the transbronchial lung biopsy showed a thickened interstitium (reticular fibers). The bronchoalveolar lavage (BAL)

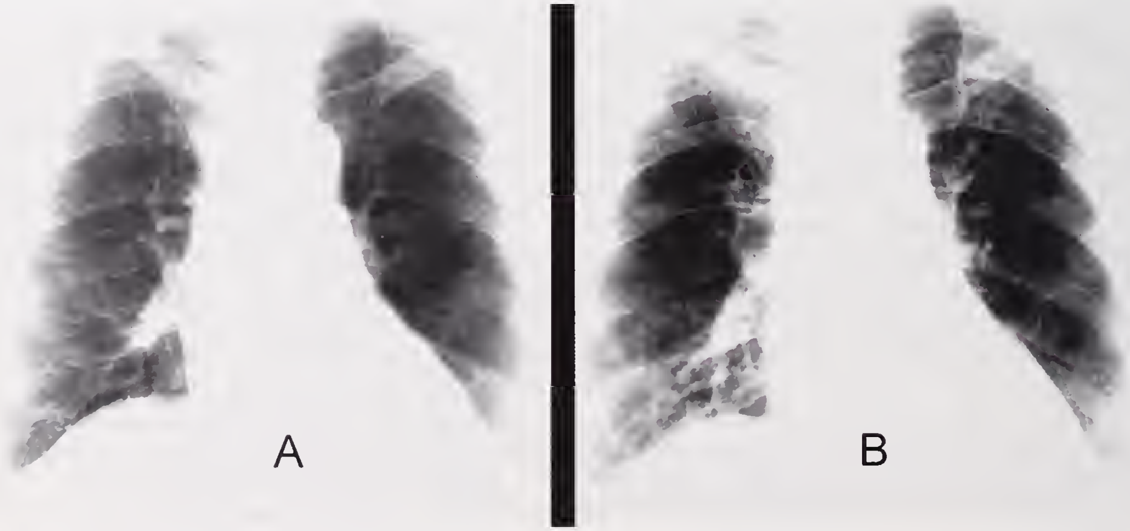

Fig. A. Normal chest x-ray at the time of admission. **B.** Chest x-ray after 3 months of mesalamine therapy revealed accentuation of pulmonary reticulum. The patient complained of cough and dyspnea.

showed a count of 60% lymphocytes and 40% monocytes. The markers for CD19 and CD3 were 0.35 and 80% respectively, and the CD4/CD8 ratio was 0.39. Mycetes, mycobacteria, or other microorganisms were not found on the lung biopsy sections and on the BAL. There was no eosinophilia. A diagnosis of interstitial pneumonitis (lymphocytic alveolitis) and mild pulmonary fibrosis, consistent with drug-induced lung disease, was made. At this time, colonoscopy did not reveal any acute inflammation and only a few small pseudopolyps.

A decision was made to reduce the daily dose of 5-ASA to 1.2 g. Corticosteroids were not reinstated. Rapid improvement of the respiratory symptoms followed without any recurrence of IBD symptoms.

Two months later, now 5 months after admission, the results of arterial blood gas determinations were within normal limits; the spirometric test was clearly improved; and a repeat chest x-ray showed a reduction of the reticular pattern. Antinuclear and anti-DNA antibody titres were absent.

Five months after the reduction of 5-ASA, now 8 months after the original admission, repeat chest radiographs, CT, bronchoscopy, arterial blood gas studies and pulmonary-function tests all showed normal results. Auto-antibodies were all negative, except for the antithyroid antibodies. BAL contained lymphocytes 30%, monocytes 70%, CD19 1.1%, CD3 69%, and a CD4/CD8 ratio of 1.05.

At the last follow-up, 4 years after the diagnosis of UC, during which time the patient was maintained on the mesalamine therapy, neither UC nor pulmonary manifestations had recurred. Of note, from the beginning of mesalamine therapy, the value of the serum amylase rose gradually to about 400 IU/L (normal values 0–220 IU/L) at 15 months, and fluctuated between 300 and 400 IU/L thereafter. The pancreatic fraction and the serum lipase remained within normal limits. At no time was there clinical or echographic evidence of pancreatitis or alterations of the salivary glands. The ANA titre at this last follow-up was reported to be positive (1:320). The other auto-antibodies, except for the antithyroid antibodies, remained negative.

Discussion

There are three different 5-ASA delivery systems. Our patient received the eudragit-coated preparation (Asacol®); with this preparation, the active drug is released in the gut by pH. A second preparation is one in which the active drug, encapsulated within ethyl cellulose-coated beads (Pentasa®), is released by agitation. The third form, olsalazine (Dipentum®), provides 2 molecules of 5-ASA when its diazo bond is broken by the action of colonic bacteria. We cannot exclude the possibility that the coating of the mesalamine preparation taken by our patient may have played a role in her reaction, since there are no data with respect to this matter.

A survey of the literature revealed 21 cases of 5-ASA-associated lung injury (4, 7–22). Also some inflammatory bowel disease (IBD) extraintestinal manifestations are lung-related (interstitial fibrosis, diffuse obstructive disease, bronchiectasis), and it is sometimes difficult to distinguish between disease-related and drug-induced causes (4). The diagnoses of drug-induced lung injury were based on various factors: the appearance of pulmonary symptoms during mesalamine therapy, the absence of any sign of recurrence of the IBD, the absence of concomitant medications, the striking clinical improvement upon removal of the drug, and for some, a history of sulfasalazine hypersensitivity. An additional factor, as in our case, is the lack of signs of recurrence of the pulmonary ADRs upon reduction of the daily dose of mesalamine. We excluded all case reports in which the pulmonary manifestations occurring during mesalamine therapy were interpreted by the author(s) to be disease-related, as well as those with pleurisy or pericarditis without concomitant involvement of the pulmonary parenchyma.

The 22 cases (including our personal observation) are summarized in the Table. There are 7 males and 15 females, with a mean age at the time of pulmonary manifestations of 46.1±17.8 years, a range of 15–72 years, and a preponderance of cases with ulcerative colitis (19/22). The interval between initiation of mesalamine treatment and onset of pulmonary symptoms varies from 2 days to 8 years. Two patients who manifested pulmonary toxicity within several days of treatment had a history of hypersensitivity to sulfasalazine (cases #1 and 2). The most frequent BAL features observed were an increased percentage of either lymphocytes or macrophages, and sometimes of eosinophils, and an inversion of the CD4+/CD8+ ratio (4 out of 7 patients).

Lung biopsies were performed in 13 patients; for 12 cases the histologic findings were consistent with the diagnosis of interstitial lung

TABLE

Published Cases of Mesalamine-Induced Pulmonary Reaction.

Case # and Reference	Type of IBD	Age[¶]	5-ASA: Daily dose/ Duration	Prior SAZ therapy/ Toxicity	EOS/ *in vitro* pertinent tests	BAL: differen./ CD4:CD8 ratio	Lung biopsy/ Findings	5-ASA stopped ↑ or n.c.	Steroids given	Lung Recovery
#1 le Gros et al.[7] 1991	UC	54/F	0.75 g/5 days	Yes/ Skin rash	No/ BD+	63% M 23% Ly/ 0.95	No	Yes	No	F
#2 Welte et al.[8] 1991	UC	67/M	1 g/10 days	Yes/ ILD	?/No	No[‡]	No[‡]	Yes	Yes	P
#3,4,5 Hesselmann et al.[9] 1991	UC	53/M	?/ ?	?/ ?	Yes/LS+	?	Yes/ILD	Yes	Yes	F[×]
	UC	42/F	?/ >9 months	Yes/ ?	No/LS+	?	Yes/ILD	Yes	Yes	F
	UC	37/F	?/ >15 months	Yes/No	No	↑ Ly/ Inv	No	Yes	Yes	F
#6 Reinoso et al.[10] 1992	UC	64/F	3.6 g/ 37 months then 3.2 g/ 7 months	Yes/ Skin rash	?/No	?	No	Yes	No	P
#7 Lagler et al.[11] 1992	UC	66/M	3 g/ 3½ months	No	No	67% Ly, 30% M/ ?	Yes/ILD	Yes	↑	F
#8,9,10 Camus et al.[4] 1993	UC, Camus #7	20/M	?/ ?	?/ ?	?/No	64% Ly/ 6.0	Yes/ILD	No	No	F
	UC, Camus #22	27/F	?/ ?	?/ ?	?/No	?	Yes/ILD	Yes	↑	F
	UC, Camus #30	24/F	?/ ?	?/ ?	?/No	?	Yes/ILD	Yes	Yes	F
#11 Honeybourne[12] 1994	UC	30/F	1.6 g/7 months	Yes/ Arthralgia	Yes/No	No	Yes/ILD	Yes	No	F
#12 Declerck et al.[13] 1994	UC	45/F	3 g/ 3 months	No	No	46% M, 39% Ly 12% E/ ?	No	Yes	No	F
#13 Muzzi et al.[14] 1995	Crohn	60/F	1.6–2.4 g/ ~ 8 years	Yes/ No	No	55% Ly, 40% M/ 1.74	No	Yes/ 3 weeks only*	No	F
#14 Bitton et al.[15] 1996	UC	32/F	4 g/9 months	Yes/ Skin rash	Yes/No	↑ M/ ?	Yes/ILD	Yes	Yes	F
#15 Sviri et al.[16] 1997	Crohn	49/M	1.5–3 g/ 3½ months	No	No	60% Ly, 10% E/ ?	Yes/ILD	Yes/ 3 months**	↑	F
#16 Lazaro et al.[17] 1997	UC	60/M	?/1 month	No	Yes/No	80% M, 10% E/ ?	Yes/ILD	Yes	No	F
#17 Pascual-Lledó et al.[18] — 1997	Crohn	64/F	3 g/2 months	No	No	↑ Ly, ↑ E/ Inv	Yes/ negative	Yes	n.c.	F

Case # and Reference	Type of IBD	Age ¶	5-ASA: Daily dose/ Duration	Prior SAZ therapy/ Toxicity	EOS/ *in vitro* pertinent tests	BAL: differen./ CD4:CD8 ratio	Lung biopsy/ Findings	5-ASA stopped ↑ or n.c.	Steroids given	Lung Recovery
#18 Sesin et al.[19] 1998	UC	72/F	1.6–2.4 g/ 3 months	No	No	No	No	Yes	No	F
#19 Tanigawa et al.[20] 1999	UC	35/F	1.5 g/ 40 days	No	Yes/LS+	49% Ly, 43% M, 7.5% E/ 2.09	Yes/ILD	Yes	No	F
#20 Guslandi [21] 1999	UC	29/F	3 g/2 days	No	No	No	No	Yes/ 3weeks ****	Yes	F†
#21 Facchini et al. [22] 1999	UC	15/M	2.8 g/ 4 months	No	No	No	No	Yes	↑	F
#22 Personal Observation	UC	70/F	2.4 g/ 3 months	No	No	60% Ly, 40% M/ 0.39	Yes/ILD	No***	No	F

BAL = bronchoalveolar lavage; BD = basophil degranulation test; E = eosinophils; EOS = peripheral eosinophilia; F = full; ILD = interstitial lung disease; Inv = inversion of CD4+/CD8+ ratio; LS = lymphocyte stimulation test; Ly = lymphocytes; M = macrophages/monocytes; P = partial; SAZ = sulfasalazine; ? = data absent/information missing; ↑= increased; n.c. = no change-continued same dosage.

¶ Age at time of pulmonary symptoms.

‡ But peripheral eosinophilia, lymphocytic and eosinophilic alveolitis on BAL, and ILD on lung biopsy were reported during sulphasalazine therapy, which was discontinued 7 m earlier.

× After apparent recovery, patient had incidental finding of lung cancer.

* After a 3-week interruption, 5-ASA was resumed at the same dose, eliciting no adverse reactions.

** After a 3-month interruption, while receiving steroids, 5-ASA (4 g/day) was resumed, eliciting, 48 hrs later, pulmonary symptoms.

*** But halved the dose of 5-ASA.

**** After a 3-week interruption, 5-ASA was resumed (0.5 g/day for 5 days and 1g/day for 2 days), eliciting pulmonary symptoms.

† The patient had only pulmonary symptoms but no radiological alterations.

disease. Only normal tissue was seen in the remaining patient. The preponderance of ILD contrasts with the variety of pulmonary complications secondary to IBD; these include, in addition, tracheal obstruction, chronic bronchitis, chronic bronchial suppuration, bronchiectasis, chronic bronchiolitis, diffuse lung disease, and necrotic parenchymal nodules (4).

The prognosis in cases of mesalamine-induced pulmonary ADR is good; in contrast to cases of sulfasalazine-induced lung injuries, no deaths have been reported.

As can be seen from the Table, once pulmonary manifestations were suspected to be mesalamine-induced, a majority of the authors opted to withdraw the drug, and half instituted or continued to use corticosteroids at higher doses, probably assuming that toxicity was due to an allergic reaction and was not dose-dependent. Yet, how strong is the basis for assuming that mesalamine-induced pulmonary injury is due to a hypersensitivity reaction? Two findings from the data support the view that, in some cases, the ADRs are not immunologically mediated.

First, in one patient a rechallenge clearly did not elicit a recurrence of ADRs. In two other patients, a continuation of the mesalamine therapy (at the same or lower dose) did not elicit a recurrence of the ADR. A rechallenge with mesalamine was tried in three other patients. In one of these (#15), after a 3-month interruption while receiving steroids, 5-ASA at higher doses (4 g/d) was resumed, eliciting a recurrence of the pulmonary symptoms 48 hrs later. In another patient (#20), after a 3-week interval, mesalamine was restarted at 500 mg daily for 5 days, without a reaction. Two days after the dosage was increased (1000 mg/day), the patient exhibited respiratory distress. In contrast, the third patient (#13), after a 3-week interval, resumed 5-ASA at the same dose (1.6 g/d), without corticosteroids. No adverse reactions were experienced. Laboratory test values remained in the normal range. While technically not subject to rechallenge, our patient and one of the patients of Camus et al. (#8) reacted similarly to patient #13. Camus' patient was diagnosed as having an ILD while receiving mesalamine. Because he was complaining of only mild pulmonary symptoms, it was decided to continue the 5-ASA treatment at the same dose, and although steroids were not added, he recovered completely over the following two months.

Second, maintenance doses of corticosteroids did not prevent drug-induced pneumonitis in four patients (cases #7, 9, 17 and 21). In addition, the patient reported by Sviri et al. (#15), failed to improve after high doses of hydrocortisone were administered intravenously (300 mg/d for 3 days), and mesalamine therapy was discontinued. The outcome in about 50% of the patients who were not treated with corticosteroids once the ADRs became evident was identical to that of those who were treated with corticosteroids.

Any conclusion on pulmonary ADR is subject to the limitation that the data are obtained solely from case reports. It is evident from the above observations that several case reports do not fit into the basic immunologic parameters and that, for some, mesalamine-induced toxicity appears to be dose-dependent. Although the essential elements of pathogenesis are unknown (23), we advance the hypothesis that there exist two mechanisms, probably interdependent, for the pulmonary ADR: one is a direct, dose-dependent toxicity mechanism, the other is immunologically mediated. Martin (24) has suggested the same for amiodarone-induced pulmonary injury. Whether such a dual mechanism can be extended to other ADRs is an interesting question that needs to be researched.

If our conclusions are correct, then a rethinking of ADR classifications might be in order. Patterson et al. (25) — as modified by DeSwarte (26) and Blass and deShazo (27) — have devised a classification which groups ADRs into two major categories: predictable and unpredictable reactions. The predictable ADRs include toxicity from overdose and side effects and are dose- or concentration-dependent. The unpredictable ADRs include reactions with a known or presumed immunological basis and are typically dose-independent. These reactions, although unpredictable, result in predictable patterns of organ-specific (skin, lung, liver, heart, etc.) or systemic hypersensitivity that usually recur on subsequent exposure to the drug (28). The mechanisms whereby such apparent immune activation occurs remain speculative. Once a drug-induced pulmonary injury is labeled as a hypersensitivity reaction it will be classified in the "unpredictable" category (29). For some of the reactions it is possible to demonstrate a dose-dependency, and it might be more correct to classify these among the "predictable" group, despite their rarity.

Moreover, it is interesting to note the positive ANA titre for our patient four years after the beginning of mesalamine therapy. However, whether her ADR was an autoimmune response or drug-induced is unclear, since this patient also was found to have autoimmune hypothyroidism.

Summary

In the cases reviewed, pulmonary manifestations associated with mesalamine-induced ADRs usually regressed completely following whatever therapeutic choices were instituted. There were no deaths. These results suggest a rethinking of the therapeutic approach for some patients whose pulmonary manifestations improve following a reduction in their dose of mesalamine (e.g., to 0.8 – 1.2 g/d). If there is no ADR, it may be reasonable to continue the use of mesalamine at this dose. The addition of corticosteroids does not seem to be necessary for these patients.

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Pneumococcal Vaccine Failure in an HIV-Infected Patient with Fatal Pneumococcal Sepsis and HCV-Related Cirrhosis

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Abstract

Pneumoccocal vaccination of HIV-positive individuals is recommended to prevent pneumococcal infection. We present a case of a 44-year-old HIV-infected male who came to the emergency room with bacterial pneumonia and sepsis. The patient also had a history of HBV and HCV infection. He expired in the emergency room and blood cultures were positive for *Streptococcus pneumoniae*. The autopsy confirmed the clinical diagnosis and, in addition, hepatitis C-related cirrhosis and splenic abnormalities. The patient had no history of opportunistic infections. His CD4 count 3 months prior to coming to the emergency room was 216 cells/μL with a viral load of 1,270 copies/mL. The patient had received Pneumovax^{TM} two years before his death. The organism isolated from blood cultures was *Streptococcus pneumoniae* isotype 3, a strain included in Pneumovax. This is a case of pneumococcal vaccine failure with a fatal outcome in a person with an HIV infection and hepatitis C-related liver cirrhosis.

Key Words: *S. pneumoniae*, isotype 3, vaccine, Pneumovax, HIV, pneumonia, sepsis, HCV, cirrhosis.

Introduction

Bacterial pneumonia, particularly secondary to *Streptococcus pneumoniae,* is a common and life-threatening manifestation of AIDS (1 – 3). A commonly used polysaccharide vaccine, Pneumovax^{TM}, represents antigens of 23 different strains of *S. pneumoniae* and covers about 82 – 85% of all pathogenic strains (1, 3). Vaccination against *S. pneumoniae* is recommended for patients with HIV infection (4), but it has been shown that such patients have a variable response to pneumococcal vaccine (5). In fact, at least 6 cases of vaccine failure have been reported in people with HIV infection and in patients with AIDS (6 – 11). This is a report of a case of Pneumovax failure in a previously asymptomatic HIV-positive person with concurrent hepatitis C-related cirrhosis, who expired secondary to pneumococcal sepsis and pneumonia.

Case

A 44-year-old Caucasian male presented in April 1997 to the emergency room (ER) with a 6-day history of violent shaking chills, night sweat and malaise; he reported shortness of breath, occasional blood-tinged sputum and pleuritic chest pain for three days. The patient was known to have been HIV-positive for 8 years, with risk factors including intravenous drug abuse. He had received medical care at the infectious disease clinic in this hospital. At his last appointment, 3 months prior to his presentation to the ER, he had a CD4 cell count of 216 cells/μL (17%) and a CD4/8 ratio of 0.27; 6 months prior to presenting to the ER, his CD4 count was 235 cells/μL (16%) and his viral load was 1270 copies/mL. He had a history of chronic sinusitis and hepatitis C and a complete recovery from hepatitis B infection; he had never suffered from the opportunistic infections common in AIDS. For two years prior to his ER presentation, he had been taking zidovudine, lamivudine and trimethoprim-sulfamethoxazole.

In the ER the patient was poorly cooperative, appeared pale and coughed occasionally. His respiratory rate was 40/min. The patient was hypotensive (BP 91/60 mm Hg) and his heart rate was 114/min. He was afebrile, hypoxemic and oliguric. The breath sounds over the right lung field were decreased, and the chest X-ray showed an infiltrate of the entire right lung. Septic shock with severe bacterial pneumonia was diagnosed. Ceftazidime, erythromycin, trimethoprim-sulfamethoxazole and intravenous hydration were administered. Lab-

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oratory studies showed thrombocytopenia, toxic granulation of leukocytes, slight target cells and crenated cells on the blood smear, and acute renal failure. The prothrombin time was prolonged (14.5 seconds) and the patient had increases in AST (234 U/L) and ALT (94 U/L). The serum total protein and albumin were 5.3 and 2.1 gm/dL respectively. Subsequent studies showed worsening of hypoxemia, metabolic acidosis and an elevated lactate level. The patient required orotracheal intubation and mechanical ventilation. About 11 hours after presenting to the ER, the patient developed recurrent ventricular tachycardia and expired.

An autopsy showed lobar pneumonia, pleural effusion, ascites, cardiomegaly with unremarkable valves, esophageal varices, splenomegaly and hepatomegaly with liver cirrhosis. Histopathology of the lungs revealed sheets of acute and chronic inflammatory cells diffusely filling the alveolar spaces, intra-alveolar edema and capillary congestion. Histopathology of the liver revealed cirrhotic micronodules surrounded by bridging bands of fibrosis with portal ductular proliferation and moderately periductual lymphocytic infiltrate. Histopathology of the spleen showed marked sinusoidal congestion with mild depletion of the white pulp. Lymph nodes showed mild follicular depletion. With the exception of minimal aseptic leptomeningitis, the neuropathological findings were unremarkable.

Streptococcus pneumoniae was cultured from various blood samples. The organism was sensitive to penicillin, chloramphenicol, vancomycin and erythromycin. Isotyping confirmed *S. pneumoniae*, strain type 3.

Subsequent review of the infectious disease clinic chart revealed that the patient had received Pneumovax^{TM} (Merck, Sharp and Dhome) and vaccination for influenza virus two years before his death. The polyvalent pneumococcal vaccine also includes isotype 3. At the time of vaccination his CD4 count was 250 cells/µL (19%); he was prescribed zidovudine, lamivudine and trimethoprim-sulfamethoxazole. Over the subsequent 2 years there was a transient increase of his CD4-count to a maximum of 370 cells/µL (22%) and then a slow decline.

Discussion

We present a case of an HIV-infected host who quickly succumbed after the onset of pneumococcal pneumonia despite having received Pneumovax some two years earlier. Six cases have been previously reported with pneumococcal vaccine failures in people with HIV or patients with AIDS (6–11). Previous cases included one patient with a CD4 count of 500 cells/µL, who expired with pneumococcal meningitis about 18 months after vaccination. The isolate identified was *S. pneumoniae* isotype 9, which is included in the vaccine (6). Another case involved a patient with a CD4 count of 141 cells/µL at the time of vaccination; this patient succumbed to pneumococcal meningitis with isotype 3 approximately 13 months after vaccination (7). A further case concerns a patient with a helper T-cell count of 13% and a helper/suppressor ratio of 0.22; the patient succumbed to pneumonia, with isolation of *S. pneumoniae* type 4, *Pneumocystis carinii* and *Legionella pneumophila*. Evaluation of stored serum specimen from all three patients showed poor antibody response to vaccination (6–8). Unfortunately, sera needed to examine the post-vaccination antibody response were not available in our patient. The other reports (9–11) of pneumococcal vaccine failure in HIV-infected persons do not give details about serotype of the organism and immune status of the host.

Several lines of evidence suggest a humoral defect in HIV-infected people; they have been reported to generate poor antibody response to pneumococcal vaccines (5,12–15). Sera obtained from HIV-negative adults vaccinated with a 23-valent vaccine showed increased *in vitro* killing activity against certain *S. pneumoniae* isotypes, when compared with the sera of HIV-positive patients with actual pneumococcal infections (9). Furthermore, only 67% of the HIV-infected patients to whom Pneumovax had been administered showed a significant increase of specific IgG and IgG2 one month after vaccination. In these patients, specific antibodies returned to prevaccination levels 12 months after vaccination (15). This indicates that prophylaxis Pneumovax in HIV-infected patients is transitory, with a significant number of such patients being non-responders (15). The anti-pneumococcal antibody response seems to be regulated by T-cell derived cytokines (16). Similarly, measles vaccination yields lower antibody response in vaccinated HIV-positive children than in vaccinated healthy children (17). Finally, patients with AIDS have been reported to generate a poor B-cell response to pneumococcal polysaccharide (tetradecavalent) and protein (keyhole-limpet hemocyanin) (14). The post-Pneumovax antibody response to isotype 3 is particularly impaired in HIV-positive patients (12). This is especially serious, since isotype 3 has a high case fatality rate even with antimicrobial therapy (18). Identification of the isotype in reports of pneumococcal vaccine failure in HIV infections or AIDS include *S. pneumoniae* isotype 3 (this report and ref. 7), 4 (ref. 8), 6 (ref. 11) and 9 (refs. 6 and 11).

Our case demonstrates the potential seriousness of pneumococcal infection in patients with HIV infection. Pneumococcal bacteremia has a particularly high mortality in AIDS patients (2). A previous report indicated a good outcome of pneumococcal bacteremia in HIV-infected individuals without AIDS compared to those with AIDS (19). While we believe that our patient did not fit the exact criteria for AIDS some 3 months earlier, we cannot exclude the possibility that, at the time of his admission, the CD4 count had dropped below 200 cells/μL. Thus, he might have fulfilled the diagnostic criteria for AIDS. In addition, he had hepatitis C liver cirrhosis with depletion of the lymphocyte population in the spleen and lymph nodes, and thus might have been additionally immunocompromised. Prior studies have showed the essential role of the spleen in the clearance of pneumococci from the bloodstream (20, 21). In the previously described case, even though the CD4 count was reported as 500 cells/μL, information on the CD4 percentage was missing (6). It has been shown that CD4 percentage shows less variability and has greater prognostic significance than the absolute CD4 count (22, 23), particularly in the setting of splenectomy in HIV-infected patients (24). Comorbidities placing the patient at risk for pneumococcal infections cannot be ruled out in the absence of an autopsy. Our patient had chronic sinusitis and may have been colonized with *S. pneumoniae*, with an increase in risk for recurrent infections.

The patient presented here had, in addition, autopsy-proven hepatic cirrhosis, most likely due to hepatitis C virus infection. Hepatitis C virus infection is a common infection in HIV-positive patients (25–27). Resistance to *S. pneumoniae* and specific antibody response has been studied in animal models (28, 29). Cirrhotic rats are able to generate a specific type 3 pneumococcal capsular polysaccharide antibody response (29) which is even higher than in non-cirrhotic control animals. However, challenge with type 3 pneumococci was associated with a higher mortality in vaccinated cirrhotic rats than in control animals, and elicited a greater post-challenge response in control animals than in cirrhotic animals. Thus "the increased serum concentrations of functional, type-specific anticapsular antibody in vaccinated cirrhotic rats does not reverse their impaired resistance to type 3 pneumococcal pneumonia" (29). Moreover, compared to control animals, cirrhotic rats display decreased phagocytosis of *S. pneumoniae* by polymorphonuclear leukoyctes in the lung and increased phagocytosis by alveolar macrophages (30). Cytokines and serum complement levels are altered in cirrhotic animals and patients (28, 31). These mechanisms might play a role in patients with HCV-related liver cirrhosis and might be complicated with concurrent HIV-infection as in our patient. However, very little is known about pathogenesis of bacterial infections in concurrent HIV/HCV infection.

Recent reports show that influenza virus impairs immune function and that influenza infection may precede severe pneumococcal pneumonia in previously healthy children (32). There is no evidence that our patient had a concurrent influenza infection. He received his last influenza vaccination 2 years prior to the presentation.

Furthermore, zidovudine has been reported to improve the response to pneumococcal vaccine in persons with AIDS (33, 34). At the time of vaccination, our patient was prescribed zidovudine and lamivudine. A previously reported case of pneumococcal vaccine failure received zidovudine 10 months after Pneumovax (7); antiretroviral therapy was not mentioned in other reports of pneumococcal vaccine failure (6, 8). The temporal relation of anti-retroviral therapy and vaccination may influence the degree of antibody response to the vaccine. Our patient had not received protease inhibitors or non-nucleoside reverse transcriptase inhibitors. These medications, used in various combinations, have been shown to restore general immune competence (23) and to decrease morbidity and mortality in patients with AIDS (35). It is worthwhile exploring whether Pneumovax response increases with the use of these potent antiretroviral combinations. One might consider the optimal timing of Pneumovax administration in relation to the initiation of antiretroviral therapy.

Pneumococcal vaccine failure is particularly serious, since drug-resistant pneumococci have become more prevalent in recent years (36).

In the future, monitoring of the antibody response before and after vaccination might help to identify a subpopulation of HIV-infected people who show a low antibody response. Improved vaccines and vaccine schedules, restoring immune function with advanced anti-retroviral therapies, and revaccination should all be considered, to prevent and/or reduce the morbidity and mortality of HIV-infected individuals with pneumococcal infections.

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Ulcerative Colitis and Sarcoidosis

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Abstract

A 38-year-old woman with ulcerative colitis subsequently developed sarcoidosis. After ten years of recurrent episodes of colitis, she had presented with respiratory symptoms. The diagnosis of sarcoidosis was confirmed by mediastinal lymph node biopsy. Her respiratory symptoms gradually resolved without any specific treatment. Within the remission period of sarcoidosis, she underwent uneventful subtotal colectomy due to refractory colitis. Alterations in immune function and genetic susceptibility have been suggested to be present in both ulcerative colitis and sarcoidosis. However, the occurrence of both in the same patient has been rare. This is only the nineteenth case reported in the literature.

Key Words: Ulcerative colitis, sarcoidosis, autoimmune, human leukocyte antigen.

Introduction

THE ASSOCIATION of ulcerative colitis and sarcoidosis has been reported in the literature in only eighteen patients (1–9). The authors report another patient who was diagnosed with both conditions. While the sarcoidosis was in remission, she presented with a severe relapse of ulcerative colitis refractory to medical treatment; it subsequently required subtotal colectomy. The relationship between these two diseases is still unclear, but cellular immunity as well as genetic susceptibility may share an important role in the development of both. The course of each disease seems to be independent and unpredictable. Human leukocyte antigen (HLA) analyses were performed to evaluate a possible genetic correlation of both diseases. The results of this evaluation indicated that the patient's genetic patterns differed from those reported previously for other patients with both conditions.

Case Report

A 38-year-old Caucasian woman, a nonsmoker, had a fourteen-year history of ulcerative colitis. At the age of 24, she had first noted abdominal cramps and bloody diarrhea; sigmoidoscopy and biopsy were consistent with the diagnosis of ulcerative colitis. After three months of sulfasalazine and corticosteroid enemas, her colitic symptoms began to improve. Despite the maintenance dose of sulfasalazine, she continued to experience at least one or two exacerbations per year, which were controlled by increasing the dose of sulfasalazine. She has no familial history of inflammatory bowel disease.

At the age of 34, she developed a chronic productive cough, low-grade fever, and shortness of breath along with her active colitic symptoms. She also experienced a 10 kg weight loss. She had no family history of pulmonary disease or exposure to occupation toxins. Complete blood count and liver function tests were within normal limits. Erythrocyte sedimentation rate was elevated. Sequential chest x-rays revealed an infiltration in the right middle and lower lobes, which progressed to multiple bilateral nodular infiltration, despite treatment with antibiotics for one month. The purified protein derivative (PPD) skin test and serum anti-nuclear antibodies (ANA) were both negative. Liver enzymes which had been elevated returned to normal after 6-mercaptopurine was discontinued. Chest CT scan revealed a slightly enlarged subcarinal lymph node and multiple bilateral pulmonary nodules, the largest of which was in the left mid-lung field and demonstrated an air-bronchogram and a cavitary lesion. Bronchoscopic examination was negative. CT-guided needle biopsy of the right lower lung revealed non-necrotizing granulomas, with numerous histiocytes and some multinucleated giant cells, which was compatible with sarcoidosis. Mediastinoscopic biopsy of the hilar lymph node revealed non-caseating granulomas with Schaumann bodies, also consistent with sarcoidosis. Malignant cells, acid-fast bacilli, and fungi were not seen and acid-

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fast bacilli, yeast, and fungi were not cultured from the tissue. The patient's respiratory symptoms and follow-up chest x-ray improved without specific treatment. Her concurrent, active ulcerative colitis responded to treatment with increased doses of sulfasalazine and corticosteroid enemas. These medications were then reduced to maintenance doses, but three months later she developed a severe exacerbation of her colitis, which required hospitalization and intravenous corticosteroid, cyclosporine and 6-mercaptopurine.

After several mild exacerbations, at age 36 she developed a severe relapse of colitis. Once the diagnosis of toxic colitis was made, high doses of steroids and cyclosporine were administered intravenously, but without a significant improvement. Subtotal colectomy and end ileostomy were performed. Pathology confirmed universal, fulminant, chronic ulcerative colitis with toxic dilatation. The patient recovered and was discharged on postoperative day 7 without complication.

HLA analyses revealed HLA-A2, A28, B44 and HLA-B27. HLA-B8 and DR3 were not found.

Discussion

Unexplained bronchopulmonary disease associated with inflammatory bowel disease was reported by Kraft et al. (10) in 1976. They described six patients who developed severe, unexplainable bronchopulmonary disease from 3–13 years after the onset of nonspecific inflammatory bowel disease of the colon. Bronchiectasis was identified in four, obstructive disease in five, and chronic bronchitis in all six. Abnormal pulmonary function testing has been reported in patients with ulcerative colitis (11, 12); however, no definitive etiology has been elucidated. In one study, two patients with ulcerative colitis were shown to have nonspecific pulmonary vasculitis (13, 14). Other causes of pulmonary pathology in patients with ulcerative colitis include sulfasalazine-induced lung disease (15).

Sarcoidosis is seen in all races, with a slight female predominance. It is characterized by the presence of T lymphocytes and mononuclear phagocytes, noncaseating granulomas, and cervical lymphadenopathy. While the lung is most commonly affected, other organ systems also may be involved. Papadopoulos et al. (16) reported that there was a greater incidence of autoimmune diseases in patients with sarcoidosis. These included the autoimmune thyroid disease and polyglandular autoimmune syndrome type 3 (16). They suggested that HLA-linked genetic susceptibility (HLA-B8/DR3) might predispose these patients to the development of autoimmune diseases. Yoshioka et al. reported a patient with ulcerative colitis who subsequently developed sarcoidosis and IDDM (insulin-dependent diabetes mellitus), which has been reported to be associated with HLA-DR2/DR4 (8).

Cox and McCrea (17) also reported a patient who had Sjögren's syndrome, sarcoidosis, and ulcerative colitis, in whom gastric autoantibodies were found. They suggested the more extensive acronym TOASSUC (thyroiditis, other autoimmunity, Sjögren's syndrome and ulcerative colitis).

Cohen and Sahn (18) reviewed five major clinicopathologic categories of respiratory involvement that have been described with ulcerative colitis: (a) airway disease, including subglottic stenosis, chronic bronchitis, chronic bronchial suppuration, bronchiectasis, and chronic bronchiolitis; (b) interstitial lung disease, including bronchiolitis obliterans with organizing pneumonia, unspecified interstitial lung disease, and pulmonary infiltrates and eosinophilia; (c) necrobiotic parenchymal nodules; (d) serositis with pleural or pericardial effusions; and (e) pulmonary vascular disease, including vasculitis and pulmonary embolism. Many patients (43–63%) with ulcerative colitis reported in the literature have had airway disease (19–23), with chronic bronchitis and bronchiectasis being the most common, 21% and 25%, respectively (24).

The association of ulcerative colitis and sarcoidosis has been reported in the literature. Each disease is believed to be mediated by an alteration in the body's immune function, but the definitive etiology still cannot be elucidated. Barr et al. (5) reported a higher frequency of the HLA-B8 and DR3 haplotypes in three of the eight patients (38%) who harbored both diseases. Cottone et al. (24) described the frequencies of these haplotypes in healthy persons to be 28%, while in patients with either ulcerative colitis or sarcoidosis alone it was 21% and 22% respectively. Rubinstein and Baum (6) reported three instances of ulcerative colitis and sarcoidosis appearing together and surmised that a number of immunologic factors may be present in one or both diseases. They speculated that the immunologic responses might be related to enhanced activity of circulatory killer and natural killer lymphocytes, an increased number of T helper lymphocytes in sites of disease, and the presence of circulating immune complexes and autoantibodies.

Our patient does not carry HLA-B8/DR3 as described in the previously mentioned reports; however, we have determined that our patient carries HLA-A2, A28, B44 and HLA-B27. The relationship of these findings to proven ulcerative colitis and sarcoidosis in this patient is uncertain. While the pathogenesis of both sarcoidosis and ulcerative colitis is unknown, both conditions may yet be shown to be mediated by some genetic susceptibility in immune responsiveness. Ulcerative colitis and sarcoidosis are sometimes seen in patients who have other autoimmune diseases such as Sjögren's syndrome and autoimmune thyroiditis. The occurrence of sarcoidosis and Crohn's colitis together has been reported as well (25). While increased cellular immunity, circulating immunocomplexes and autoantibodies may play a role in the pathogenesis of both diseases, each disease in our patient followed an independent course.

Our case brings to nineteen the total number of patients who have been reported to have both diseases. The adjusted prevalence rate of ulcerative colitis in Olmsted County, MN on January 1, 1991 was 229 cases per 100,000 (26) and the prevalence rate of sarcoidosis in the United States was 10–40 cases per 100,000 (27). The coexistence of both diseases in the same patient by chance can be calculated from these data to range from 2–9 cases per 10 million people. It would appear that the number of cases in which ulcerative colitis and sarcoidosis coexist in the same patient has not exceeded an association by chance. Such a conclusion necessarily depends on the reliability of the prevalence data in a given population. More data are certainly needed to establish an etiologic association between ulcerative colitis and sarcoidosis in the same patient.

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Atypical Behçet's Syndrome in a Patient with Myelodysplastic Syndrome

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Abstract

We report the case of a 67-year-old man with myelodysplastic syndrome (MDS), who presented with fever, painless penile and groin ulcers, as well as oral and esophageal ulcerations, all of which were exquisitely responsive to corticosteroids. Some cases of Behçet's syndrome and MDS have been reported in association with trisomy 8 and HLA B51, with the pathology varying from vasculitis to acute neutrophilic inflammation. Our patient with orogenital ulcers had neither trisomy 8 nor HLA B51. Also lacking were other features typical of Behçet's syndrome, such as uveitis, vasculitis, and central nervous system abnormalities. However, his response to corticosteroids on the initial presentation and subsequent episodes was dramatic. Esophageal ulcerations have not been described in Behçet's syndrome. In this respect, our patient was unique.

Key Words: Behçet's syndrome, myelodysplastic syndrome.

Introduction

NAMED AFTER THE TURKISH DERMATOLOGIST who first described it, Behçet's syndrome is characterized by recurrent orogenital ulcers, central nervous system abnormalities (CNS), arthritis, vasculitis and uveitis. The etiology of Behçet's syndrome is unknown. The course is prolonged and punctuated with remissions and exacerbations. The prevalence varies from 1:10,000 in Japan to 1:500,000 in North America and Europe. It is more common among young adults, more severe forms occurring in males than in females. Since the main pathologic lesion is vasculitis, and circulating autoantibodies to oral mucous membrane have been found in 50% of cases, it is suggested that Behçet's syndrome is an autoimmune disease (1). The ulcers may be shallow or deep, may occur singly or in crops, and are usually painful but heal without scars in approximately two weeks. The genital ulcers resemble the oral ones. Clinical diagnostic criteria include recurrent oral ulceration plus two of the following: recurrent genital ulcers, eye lesions, skin lesions and pathergy test. Hypopyon uveitis is the hallmark of eye involvement in Behçet's syndrome, but occurs uncommonly. The arthritis of Behçet's syndrome is nondeforming and usually affects the knees and ankles. CNS involvement occurs more frequently in northern Europe and the United States (2).

Case Report

A 67-year-old black man presented with complaints of painless penile ulcers and bilateral groin ulcers of four days' duration. He had had myelomonocytic leukemia for six years, and suffered from hypertension, insulin-requiring diabetes mellitus (IRDM), and peptic ulcer disease. The patient noted the penile and groin ulcers incidentally while bathing. He denied pain, itching, oozing, or bleeding from the ulcers and had no cardiovascular, respiratory, urinary, or gastrointestinal complaints. He also denied fever, chills, anorexia, and loss of weight but claimed that little bumps appeared all over his body from time to time and disappeared on their own, sometimes breaking into small ulcers. The patient had been hospitalized for oral ulcers in 1992 and treated for arthritis

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of the acromioclavicular joints in 1993. He had a tubulocolonic adenoma removed in 1994 and had a left foot ulcer in 1996. He was taking captopril, isophane insulin suspension, sucralfate, and regular insulin and had received erythropoietin and granulocyte colony-stimulating factor (G-CSF) a year earlier for his myelodysplastic syndrome (MDS). He denied allergies, smoking, alcohol use, drug abuse, and sexually transmitted diseases. The family history was noncontributory.

The patient was a well-built man with mild pallor. His blood pressure was 110/85 mmHg, heart rate 84 beats per minute, temperature 98.8°F, and respiratory rate 16 per minute. Pupils were equal and reactive to light. Cardiovascular, pulmonary, neurological, abdominal, and rectal exams were unremarkable. There was no lymphadenopathy. A 5 cm x 4 cm ulcer was seen on the ventral surface of the penis near the root and a 1 cm diameter ulcer was present on the dorsum of the penis. Two 2 cm x 2 cm ulcers were present on the upper medial aspect of both thighs. The ulcers were well demarcated, without undermining, with indurated margins, mild oozing, and no slough. The patient's blood leucocyte count was $3600/mm^3$ (38% neutrophils, 28% lymphocytes and 34% monocytes), hemoglobin 8.3 g/dL, hematocrit 24.5%, mean corpuscular volume 102.8 fL and platelets $118{,}000/mm^3$. Routine blood chemistries, chest X-ray, and electrocardiogram were within normal limits.

The patient was treated with ceftriaxone, timentin, and acyclovir. On day 5 he became febrile, and on day 8 he developed oral ulcers. Direct laryngoscopy showed vesicles on the epiglottis, larynx, and posterior uvula. The differential diagnoses included Sweet's syndrome, pyoderma gangrenosum, and Fournier's gangrene. He remained febrile (103°–106°F) while receiving antibiotics. Blood cultures, Venereal Disease Research Laboratory (VDRL) test for syphilis, orogenital, bacterial, fungal, and viral cultures were negative. Gallium scan and chest X-ray were normal. Oral and penile ulcers were biopsied and showed chronic, active inflammation with no vasculitis. Bone marrow biopsy showed chronic myelomonocytic leukemia with no evidence of transformation. Erythropoietin was given and antibiotics and acyclovir were discontinued due to lack of improvement in the ulcers and fever. The patient developed extreme odynophagia and drooled saliva copiously. His hematocrit decreased to 17%. Since the patient refused blood transfusion, the dose of erythropoietin was increased from 5000 units subcutaneously to 10,000 units three times weekly for 20 days. In addition, peripheral parenteral nutrition was commenced because the patient could not eat. On the 18th day of hospitalization, oral steroids were given. Within 48 hours, the patient became afebrile, and the orogenital ulcers showed signs of improvement. However, inability to swallow persisted. Upper gastrointestinal endoscopy showed extensive severe ulceration from 20–35 cm. Esophageal biopsy was read as unremarkable squamous epithelium. Within a week of steroid therapy, the ulcers and the odynophagia were markedly improved. The patient began eating, and steroids were tapered gradually. On the 50th day of hospitalization, the patient was discharged afebrile and able to eat normally. The oral and genital ulcers had healed.

Discussion

In rare cases, Behçet's syndrome has been reported in association with myelodysplastic syndrome (3), hepatitis C (4), acute necrotizing myositis (5), Sweet's syndrome (6), and anticardiolipin antibody syndrome (7). Primary findings include recurrent orogenital ulcers, uveitis, seronegative arthritis, CNS abnormalities, vasculitis, erythema nodosum, superficial and deep thrombophlebitis, ulcerative skin lesions and a positive pathergy test. Arthritis occurs in two-thirds of patients, and ocular involvement is usually fulminant, resulting in blindness. CNS involvement encompasses cranial nerve palsies, convulsions, encephalitis, mental disturbances, spinal cord lesions and even death. Ten to thirty-seven percent of patients have occlusion of major blood vessels and aneurysms. Seven to thirty-seven percent have thrombosis of superior and inferior vena cavas (8). Pulmonary vascular involvement causes severe hemoptysis and is the cause of death in 39% of patients. Rare cases of endomyocardial fibrosis in Behçet's disease (9) and a case of abdominal aortic aneurysm with lumbar vertebral erosion have been described. Concomitant MDS with Behçet's syndrome has been described with trisomy 8 (3) and HLA B51 (10). The pathology in Behçet's syndrome is characterized by vasculitis and/or acute neutrophilic inflammation.

Although it is usually chronic, with remissions and exacerbations, Behçet's syndrome is characterized by rapid response to steroids.

Also beneficial are azathioprine, chlorambucil, and cyclosporine. While clinically meeting criteria for Behçet's syndrome, the pathology in our patient was not characteristic. The occurrence of Behçet's syndrome with MDS is unexplained. In Behçet's syndrome, there is increased production of reactive oxygen species (ROS) by neutrophils, whereas MDS is characterized by decreased production of ROS by neutrophils. In a study of ten patients with MDS and Behçet's syndrome (11), the production of ROS by neutrophils was investigated by luminol-enhanced chemiluminescence assay (CL). Of the ten patients, nine underwent cytogenetic analysis of bone marrow and seven had trisomy 8. Neutrophils taken from the patients during the active phase of Behçet's syndrome demonstrated an increased CL response. The authors concluded that trisomy 8 predisposes to Behçet's syndrome in patients with MDS. Cytogenetic analysis of our patient on two different occasions did not reveal trisomy 8. A strong association has also been shown between Behçet's syndrome and HLA B51 in ethnic groups extending from the Middle East to Japan. HLA typing of our patient was negative for HLA B51. Esophageal ulcers have not been described in Behçet's syndrome. In this respect, our patient is unique.

A trial of corticosteroids was given to our patient after all cultures for bacteria, viruses, and fungi proved negative. The patient had a dramatic response, with resolution of all signs and symptoms. The use of corticosteroids should be considered in patients with a clinical picture of Behçet's syndrome even if the pathology is inconclusive. In a study conducted by the University of Istanbul (12), thalidomide was effective in resistant cases of Behçet's syndrome. Although banned globally because of its teratogenic effects, this drug may have important therapeutic uses.

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Facial Diplegia as the Presenting Manifestation of Acute Lymphoblastic Leukemia

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Abstract

A 36-year-old man with recent onset of unilateral peripheral 7th nerve paresis presented ten days later with involvement of the other side of his face. Physical examination was otherwise normal, and since blood tests and imaging were also normal, he was considered to have bilateral Bell's palsy. However, unexpected headaches and worsening of the paresis led to a gallium-67 scan which revealed uptake in the mediastinum. A repeat lumbar puncture revealed cells which were identified as lymphoblasts. T-cell acute lymphoblastic leukemia (T-ALL) was diagnosed, although the peripheral blood smear was normal. The differential diagnosis of bilateral 7th nerve palsy and of mononuclear cerebrospinal fluid pleocytosis is discussed, as well as this rare central nervous system presentation of acute leukemia.

Key Words: Acute lymphoblastic leukemia, Bell's palsy, cerebrospinal fluid, cranial seventh nerve, facial diplegia.

Introduction

PERIPHERAL CRANIAL NERVE AFFLICTIONS usually have a benign cause. Thus, trigeminal neuralgia is most commonly a primary disorder; only rarely is it a secondary disorder due to a systemic disease. The same is true of peripheral 7th nerve palsy, which almost always occurs in the setting of "idiopathic" Bell's palsy. However, the following report highlights that this illness can be far more ominous despite a misleadingly normal examination and laboratory test results. In particular, bilateral facial palsy is an uncommon occurrence and may have diverse etiologies (1). Occasionally it can be the presenting symptom of an occult systemic disease and present a considerable diagnostic challenge.

Case Report

A healthy 36-year-old farmer woke up with right hemifacial pain and asymmetry, diagnosed as Bell's palsy. However, he continued to suffer from intermittent pain over the right side of his face and around the eye, which radiated to the right occipital area and the posterior aspect of the neck. Ten days later the left side of the face was affected, and the patient was admitted with bilateral complete facial paralysis, complaining that he could neither smile nor smoke. Physical examination revealed only bilateral peripheral 7th nerve palsies. He had no stiff neck or other notable neurological findings on repeated examinations. The ophthalmologic exam was also normal. The ESR was 6 mm/hr, hemoglobin 14 g/dL, white blood count (WBC) 6.7 x $10^3/\mu L$ (normal differential), and platelets 144 x $10^3/\mu L$. Urinalysis and blood chemistry tests were normal, as were the ECG, chest X-ray, abdominal ultrasound and a head CT and MRI scans. Lumbar puncture (LP) revealed a normal pressure. The glucose value in cerebrospinal fluid (CSF) was normal, the protein was 62 mg/dL, and the WBC 0.4 x $10^3/\mu L$, of which 80% were considered to be normal mononuclear cells. Stains and cultures for microorganisms were negative as were tests for viruses. PPD was 4 mm. Serum protein immunoelectrophoresis and serum angiotensin-converting enzyme were normal. Autoantibody screen and extensive serological testing for varied infectious diseases were all negative. During evaluation, improvement in the facial palsy occurred and a tentative diagnosis of bilateral Bell's palsy was made.

The patient continued to complain of poorly localized headache and nuchal pain. His facial

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diplegia worsened. Although no other pathology was found on repeated thorough physical examination, and laboratory evaluation remained normal and unchanged, a gallium-67 scan was ordered and a repeat LP was performed. The scan revealed an area of marked uptake in the anterior mediastinum, where a longitudinal midline mass was confirmed by a chest CT scan. The mass was not easily accessible to biopsy but a bone marrow aspiration and biopsy yielded a massive infiltrate of blast cells with lobulated nuclei. The cells, analyzed using monoclonal antibodies and a laser flow cytometry system, were identified as LCA positive, CD2+, CD7+, CD5+, CD4+, CD8+, CD1+ and CD3 negative, consistent with T-cell acute lymphoblastic leukemia (T-ALL). The LP yielded 0.62 x $10^3/\mu L$ cells characterized as lymphoblasts (Fig.). A subsequent review of the patient's cranial CT scan and MRI scan with gadolinium contrast enhancement, was still considered normal by expert radiologists. However, a review of the cytology slides of the CSF fluid obtained at the initial LP, revealed that some of the cells previously identified as normal mononuclear cells were re-interpreted as lymphoblasts. These malignant cells now seen in the initial LP sample were similar in all respects to those seen in the fluid obtained on the second LP. The malignant cells were more numerous in the second LP sample.

Ten days following the patient's admission, systemic and intrathecal chemotherapy were started according to ALL-BFM 95 protocol MR1 (intermediate risk) with some modifications (high-dose cytosine arabinoside instead of methotrexate). Triple intrathecal injections of methotrexate, cytosine arabinoside and hydrocortisone were administered twice weekly until the CSF became normal; they were then continued once every two weeks, together with cranial irradiation (1800 rad). Complete remission was achieved after four weeks. Twelve months later, the patient shows no evidence of recurrence.

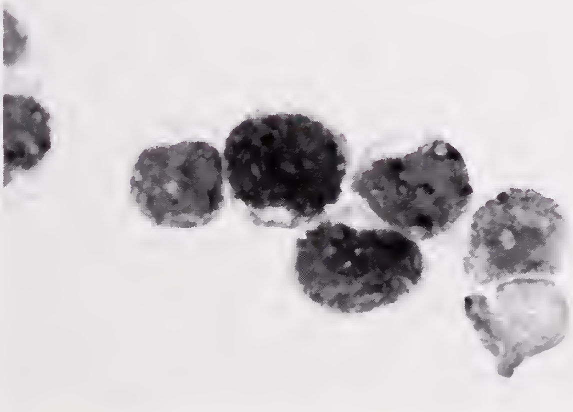

Figure. Cytocentrifuge of patient's second CSF examination showing lymphoblasts (May-Grunwald Giemsa staining, x 800).

Discussion

In *Alice in Wonderland* the Cheshire cat gradually vanished, leaving only his smile behind. Here, our patient's smile disappeared first but it soon became apparent that unless quickly treated, the patient himself might follow suit. Bell's palsy has an average annual incidence of 25 per 100,000 population (1), but simultaneous bilateral facial palsy, or facial diplegia, is decidedly uncommon, encountered in only 3 of 1000 consecutive patients with facial paralysis (2). Thus, there are very few small series of patients with bilateral 7th nerve palsy. These few patients reveal diverse causes for facial diplegia, most being benign, including bilateral Bell's palsy, atypical Guillain-Barré syndrome, and granulomatous diseases and infections such as Lyme disease, syphilis, TB meningitis, sarcoidosis, mycoplasma, herpes virus infections and HIV (1). Tumors, in particular hematological malignancies involving the meninges or tumors of the pontine area, are also important etiologies to consider, accounting for about 20% of the cases.

The sparing of other cranial nerves and long tracts in our patient, his negative initial evaluation including the normal MRI (3) and the partial spontaneous improvement which occurred at first, were all considered favorable signs in a patient who was considered to have bilateral Bell's palsy. The mononuclear cells in the first CSF were thought to be consistent with the finding of mononuclear pleocytosis seen in some cases of Bell's palsy (2, 4). This finding has many varied causes, as listed in the Table (5 – 11). In one study of 164 patients with Bell's palsy, examination of the CSF disclosed that 33% of the patients had an elevated protein level and 10% had pleocytosis (4). In another large study of 1048 patients, 10% had headache and 62% had facial pain when presenting with Bell's palsy (2). However, in our case the number of cells in the CSF was greater than expected, and facial and nuchal pain, and continued headache are distinctly unusual in patients with Bell's palsy (12). When the bilateral facial palsy worsened (it should have improved in the

TABLE

Main Causes of Predominantly Mononuclear Cells in the CSF (5–7).

Infectious

Viral infections†
    'Viral aseptic meningitis' often caused by non-polio enteroviruses, or as part of distinct diseases such as mumps, herpesvirus* infections or HIV* [reported also postvaccination against viral diseases].

Infections caused by "unusual" organisms
    Mycobacterium tuberculosis ("TB meningitis"*), *Treponema pallidum* (syphilis*), *Borrelia burgdorferi* (Lyme disease*), brucella, leptospira, *Mycoplasma pneumoniae**, rickettsiae, toxoplasma and fungi — especially *Cryptococcus neoformans**.

Parameningeal focus of infection such as brain abscess or sinusitis.

Non-infectious

Neurosarcoidosis*
    Aseptic meningitis may be the sole manifestation of neurosarcoidosis (9) in about 17% of patients.

Neoplastic* meningeal or CNS involvement
    Reported in both benign and malignant tumors, both primary and secondary — including hematological malignancies‡.

Multiple sclerosis or other demyelinating disorder.
    CSF is normal in 66% of patients; in the remainder 5–20 lymphocytes/mm^3 can be found

Behçet's disease
    Also uncommonly reported in varied autoimmune disorders including lupus*, primary Sjögren's syndrome*, polyarteritis* and in granulomatous arteritis.

Idiopathic chronic (benign) lymphocytic meningitis (11)

Guillain-Barré syndrome*
    Possibly 10–100 mononuclear cells, usually none.

Bell's palsy*
    Possibly 10–100 mononuclear cells, usually none.

*Some of these disorders may cause cranial 7th nerve palsy.
†Some patients with acute bacterial meningitis who have a low CSF WBC count (< 1000/mm^3) may have >50% mononuclear cells early in the course of their illness, but associated findings will establish the correct diagnosis. In particular, listeria monocytogenes meningitis may be confused with viral lymphocytic meningitis (8).
‡Malignant meningeal involvement is the only entity cited, where careful and expert examination of CSF cytology may itself be diagnostic (10).

case of Bell's palsy) (12), the gallium-67 scan and LP were repeated. The gallium scan was ordered in an attempt to identify a site from which pathological tissue might be biopsied (13). We had in mind the high avidity of gallium-67 for lymphomas (14), after other more benign causes of facial diplegia (such as infections) had been ruled out and brain imaging was not diagnostic. Following the abnormal results of both the gallium scintigraphy and CSF analysis, a bone marrow biopsy was done. The diagnosis of T-ALL with central nervous system presentation soon followed. In retrospect, a careful examination of the initial CSF by an expert cytologist would have yielded the correct diagnosis. The MRI, with gadolinium enhancement (which is often very useful in establishing the diagnosis of bilateral facial paralysis [3, 15]), was misleadingly normal in our patient. This demonstrates again that the most simple tests are often highly rewarding in difficult cases, provided they are meticulously performed and interpreted. However, in patients with leukemia and CNS involvement, the CSF may not reveal pathological cells in all cases. In leptomeningeal carcinomatosis, for example, the sensitivity of CSF cytology has been consistently found to range from 75–90% (15, 16).

Initial CNS involvement can be found in fewer than 1% of adult patients diagnosed with acute leukemia and is rarely documented as the presenting feature. Although the central nervous system is an important site of relapse, meningeal involvement is an uncommon pattern of presentation of leukemia. Moreover, the presence of normal peripheral blood cell and even normal bone marrow cytology may cause diagnostic delay (17). Acute leukemia, lymphoma and amyloidosis are the main hematological malignancies which may present initially as facial diplegia (1). Such presentation has been reported in the English language (18, 19) in only ten cases.

Nevertheless, this patient's presentation of isolated 7th nerve involvement and head and neck pain, is consistent with the anatomy of the facial nerve. The 7th nerve nucleus is located in the base of the pons. Central lesions are rarely so discrete as to affect only one cranial nerve nucleus. Signs implicating the brainstem as the site of the lesion would be expected if sensory, cerebellar or corticospinal pathways, or adjacent nuclei or nerves (5th, 6th) were involved. When the 7th nerve is solely affected, the lesion is most likely outside of the brainstem (20). Upon its exit from the brainstem, the 7th nerve must cross the subarachnoid space before entering the internal auditory meatus. This is the most likely site of nerve involvement in the presence of meningeal leukemia and pathological cells in the CSF, and may also explain the patient's headache and nuchal pain (21). Importantly, neuropsychiatric symptoms may also indicate malignant meningitis in patients with hematological malignancies, even when no neurologic findings are present (22).

In conclusion, our case demonstrates that unusually persistent bilateral 7th nerve palsies may indicate the presence of a serious underlying disease, such as leukemia. In these uncommon cases, a high index of suspicion and careful examination of the CSF by an experienced cytologist may lead to the correct diagnosis and rapid initiation of appropriate chemotherapy and irradiation.

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Castleman's Disease and Superior Vena Cava Thrombi:

A Rare Presentation and a Review of the Literature

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Abstract

Castleman's disease is a clinicopathological entity in which growth of lymphoid tissue is unregulated. It may present as asymptomatic involvement of one lymph node group or as a multicentric disease with systemic symptoms. Unlike localized disease, for which surgical excision is curative regardless of the histological type, multicentric disease often necessitates aggressive systemic therapy and portends a poor outcome. Superior vena caval thrombosis is an uncommon manifestation associated with Castleman's disease.

We describe a patient with this rare manifestation and present a systematic survey of the disease, based on the current literature.

Key Words: Castleman's disease, Kaposi's sarcoma, superior vena cava thrombosis.

Introduction

Castleman's disease is also known as angiofollicular lymphoid hyperplasia or giant lymph node hyperplasia, lymph nodal hamartoma and benign giant lymphoma (1, 2). It was first described in 1956 in a group of patients with localized mediastinal lymph node enlargement characterized by (1) "hyperplasia of lymphoid follicles with or without germinal center formation and capillary proliferation with endothelial hyperplasia." It is currently classified into two major subgroups: localized Castleman's disease and multicentric (disseminated) Castleman's disease (3). There are three histologic variants: hyaline-vascular, plasma cell and transitional (mixed type) (3, 4). In this article, we present a case of the hyaline-vascular type of Castleman's disease (localized) presenting with superior vena cava thrombosis, and review the literature.

Case Report

A 47-year-old woman from Guyana with no significant medical history was hospitalized because of a right lung mass on her chest roentgenogram (Fig. 1). The patient had a dry cough for two months but denied fever, shortness of breath, expectoration, chest pain, palpitation, loss of weight, loss of appetite, hemoptysis, smoking, alcohol and recreational drug use.

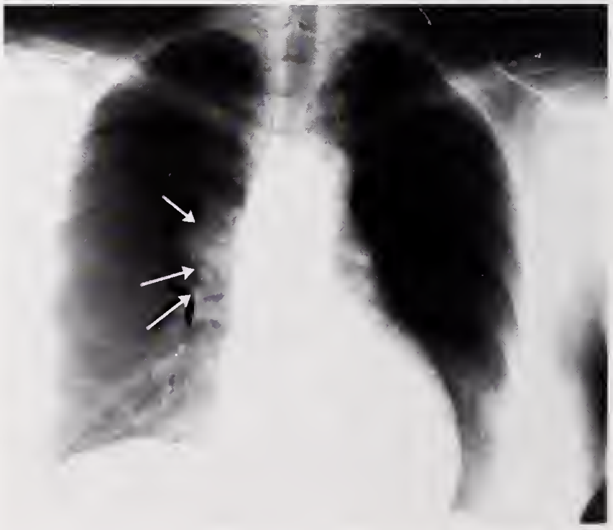

Fig. 1. Chest roentgenogram showing a suprahilar mass lateral to azygos vein.

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The physical examination was unremarkable. The patient was in no apparent distress, normotensive, afebrile, in regular sinus rhythm, and breathing normally. There was no evidence of superior vena caval obstruction. The complete blood count, routine serum chemistries and liver profile were normal. Protein C and S deficiencies, anticardiolipin antibodies and factor 5 Leiden were not found. The serum angiotensin converting enzyme (ACE) level was normal. Room air arterial blood gases (ABG) were normal. The PPD test was negative with a positive anergy panel.

The CT scan of the chest revealed a 4 – 5 cm mass representing extensive lymphadenopathy in the right hilum compressing the medial segment of the right middle lobe (Fig. 2). A large thrombus was also seen in the superior vena cava. The patient was anticoagulated with heparin (80 units/kg, followed by 18 units/kg/min) so as to maintain the PTT at 1.5 – 2 times the control value.

Heparin was withheld when it was decided that a mediastinal biopsy should be performed. Unfortunately, the tissue obtained from this biopsy attempt was not diagnostic. Heparin was then restarted after this procedure. On day 12 of heparin therapy, a superior vena caval venogram showed small round filling defects in the superior vena cava (Fig. 3). A filling defect in, and dilation of, the right brachiocephalic vein were also seen.

Heparin was discontinued in order to perform an open lung biopsy. The histopathology of this tissue was consistent with Castleman's disease of the hyaline-vascular type. Surgical resection of the right middle and upper lobe was followed by uneventful recovery. The patient is now well. No further therapy was administered.

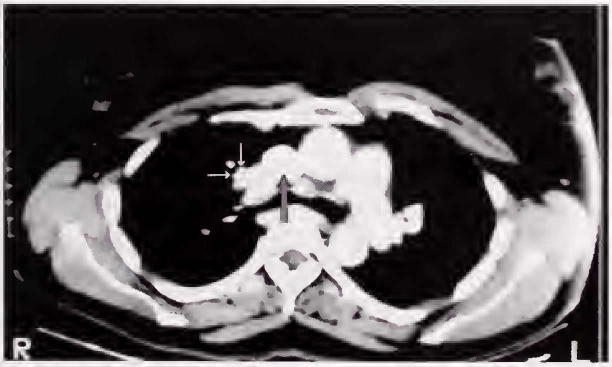

Fig. 2. Computed tomographic scan of the chest showing a mass on the right side representing lymphadenopathy (narrow arrows) and a superior vena caval thrombus (wide arrow).

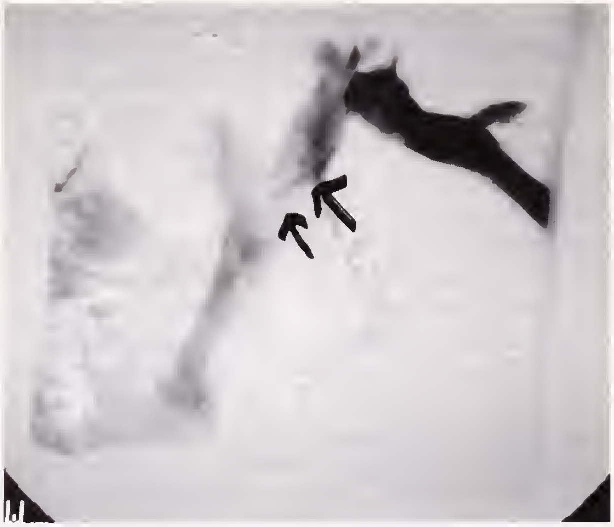

Fig. 3. Superior vena caval venogram showing a thrombus (defect) in the right brachiocephalic vein extending into the superior vena cava.

Discussion

Castleman and his colleagues (1, 5) first reported a group of patients who presented with mediastinal masses that were thought to be thymomas. Light microscopy revealed striking lymph node hypertrophy with hyalinized foci that resembled Hassall's corpuscles. In 1969, Flendrig and Schillings (6) described two histologic variants of Castleman's disease: hyaline-vascular and plasma cell. In a large review, Keller et al. (4) found that 91% of all cases of this disorder were hyaline-vascular and 9% were of the plasma-cell variety. They also described a third type: mixed cell type or hyaline-vascular plasma-cell type. These histopathologic types typically present as indolent disease confined to a single site. A more generalized lymphadenopathy (multicentric) form, accompanied by systemic symptoms, organomegaly and laboratory abnormalities, has a progressive clinical course (7).

Pathogenesis

The underlying cause of Castleman's disease is unknown; however, several theories have been formulated to account for the spectrum of associated pathologic and clinical features (8). Proposed pathogenetic mechanisms include chronic, low-grade inflammation (4), immunodeficiency (9 – 12) or autoimmunity (11) and Epstein-Barr virus (9, 13, 14), Toxoplasma, or *Mycobacterium tuberculosis* infections (2, 4). Although the evidence to support these hypotheses is scanty and speculative, the search for a unifying model of Castleman's disease has led to new insights into its pathogenesis.

Accumulating data suggest that overproduction of IL-6 by the hyperplastic lymph node plays a central role in the development of both localized and multicentric variants of Castleman's disease (15, 16). IL-6, a soluble protein secreted by several cell types, has modulating effects on immune function and hematopoiesis. It is necessary for the proliferation and maturation of B-lymphocytes into immunoglobulin-secreting plasma cells. In animal models, disregulated production of this cytokine causes abnormal plasma cell proliferation in lymph nodes and other lymphoid organs in conjunction with polyclonal hypergammaglobulinemia, a syndrome clinically and histologically indistinguishable from Castleman's disease in humans (17).

In addition, lymph nodes from patients with Castleman's disease (12) excrete large amounts of IL-6, suggesting that the inappropriate synthesis of IL-6 plays a role in the pathogenesis of this syndrome (18). Furthermore, IL-6 induces proliferation of normal endothelial cells (19) and AIDS-Kaposi sarcoma derived cell lines (20). Lastly, systemic manifestations such as fever, weakness, anemia hypergammaglobulinemia, and the acute phase response in the plasma-cell variant, can be explained on the basis of increased blood level of IL-6 (10).

The lymphoplasmacytic proliferation driven by abnormal IL-6 production may set the stage for the development of malignant lymphomas. Similarly, continued stimulation of endothelial cells through release of angiogenic factors could promote vasoproliferation and ultimately lead to the emergence of a vascular neoplasm (21).

Multicentric Castleman's disease (MCD) is associated with human herpes virus 8 (HHV-8) (22). This virus is also associated with AIDS, and AIDS-related Kaposi's sarcoma (KS), as well as primary effusion lymphoma (23). HHV-8 encodes a functional analogue of IL-6, a cytokine that promotes the growth of KS and myeloma cells. IL-6 levels are increased in the sera and lymph nodes of patients with MCD. In those patients with Castleman's disease who do not have HIV infection, HHV-8 may explain the development of Kaposi's sarcoma (24).

Histologic Features

Histologically, Castleman's disease is divided into hyaline-vascular and plasma-cell types (4). A clear separation of the two variants is not always possible, and cases with mixed histologic features occur. The hyaline-vascular type is characterized by the proliferation of small, distinctive follicles that obscure the underlying nodal architecture (4).

The follicles are surrounded by circumferentially arranged layers (onion skin) of small lymphocytes in the mantle zone, with peripherally arranged capillaries penetrating the germinal center. Frequently, the germinal centers have a characteristic whorled appearance (4). The interfollicular stroma has marked proliferation of capillaries, varying numbers of lymphocytes, and occasional plasma cells. The plasma-cell type of Castleman's disease (CD) also has numerous lymphoid follicles, but they tend to be larger, and prominent germinal centers are more typical of reactive follicular hyperplasia (2, 7).

The expanded interfollicular zones of the plasma-cell type of CD are filled with mature plasma cells which form broad sheets (2, 4). The interfollicular stroma tends to be less vascular and is mainly populated by endothelial venules. Lymph nodes may be only partially involved, and areas of uninvolved nodes show patent sinuses. Although immunohistologic staining in most cases of plasma-cell CD shows polyclonal expression of light chains in the plasma cells, a monoclonal component associated with a serum M protein occurs in rare cases (25).

Although these histologic features are characteristic, they are not specific, and "Castleman's disease-like" changes have been reported in a wide range of conditions (2), including rheumatoid arthritis, Sjögren's syndrome, phenytoin hypersensitivity, lymph node draining carcinomas, iatrogenic immunosuppression (12), and congenital or acquired immunodeficiency states, including the acquired immunodeficiency syndrome (AIDS) (2, 13, 26). Similar histologic changes reported in lymph nodes in patients with Hodgkin's disease have led to diagnostic errors (14).

Hyaline-Vascular Castleman's Disease

Most patients with the hyaline-vascular variant are asymptomatic. Some patients have compression of the tracheobronchial tree, causing dry cough and dyspnea. Recurrent infections may occur, due to local mass effect (1, 4). About 70% of the lesions are intrathoracic (4), the anterior mediastinum being the most common site. One study showed a distribution of

46% of cases in the mediastinum, 39% in the abdomen, 15% in the periphery (27). Rarely, lesions which simulate lung cancer are found within the lung fissures (4). There may be recurrent pleural effusions (4, 28). Extrathoracic lesions have been reported in the retroperitoneum, mesentery, central nervous system, orbit, and pelvis, neck, axilla, and skeletal muscles (29–32). Localized hyaline-vascular Castleman's disease appears on chest radiographs as a sharply marginated smooth or lobulated mass.

Pleural effusion is uncommon, and calcification in the mass is rare (33). On unenhanced CT images, a homogeneous or heterogeneous mass of soft-tissue attenuation is seen. Although calcification is uncommon, occurring in only 5–10% of cases (34, 35), when it is present, it is typically coarse and central in location. On CT scan or MRI, involved lymph nodes typically demonstrate homogeneous contrast enhancement (36, 37). This feature may prove helpful in distinguishing the Castleman's-disease mass from other mediastinal masses such as lymphomas or thymomas, which generally do not show any enhancement on a CT scan.

Surgical resection is the primary treatment of the hyaline-vascular variant (32), and is curative in virtually all cases. However, local recurrence has been reported after subtotal resection of the tumor. Radiation therapy has been used with varied success in patients who are poor surgical candidates or in those with unresectable lesions (38). Hyaline-vascular CD is considered benign and self-limited, with 5-year survival approaching 100% (2, 4). In very rare instances, vascular neoplasms that resemble KS develop (21). KS is more typically associated with the multicentric variant of the disease (8, 39, 40). Rarely, malignant lymphoma may occur in patients with hyaline-vascular CD. Vascular neoplasms such as KS and lymphomas may develop as long as eight years after the initial diagnosis of CD. Thus, long-term follow up is necessary (41).

Plasma-Cell Castleman's Disease

The plasma-cell type of Castleman's disease usually presents as multiple, discrete, enlarged lymph nodes (4). Patients are likely to experience fever, weight loss and pruritus during the course of their illness (4). Although such symptoms are common in the plasma-cell variant, both types of Castleman's disease may be associated with numerous clinical conditions not directly related to the tumor mass (Table 1).

Surgical resection of the hyperplastic lymph nodes often results in complete resolution of constitutional symptoms. Plasma-cell lesions are likely to occur in extrathoracic sites such as the mesentery and retroperitoneal space, or involve multiple lymphoid organs concurrently (2, 4, 8). The mediastinal masses may invade the bronchi as friable endobronchial lesions that cause bleeding during biopsy or other instrumentation (37).

Multicentric Castleman's Disease

Disseminated or multicentric Castleman's disease is currently regarded as a potentially malignant lymphoproliferative disorder associated with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal proteinemia, and skin changes) syndrome, osteosclerotic myeloma, KS, and AIDS (3, 42–44). It affects individuals of all ages, but the peak incidence is in the fifth decade of life. Women are more commonly affected than men by a ratio of 2:1. Most patients present with fever, weight loss, and weakness (3) (Table 2).

TABLE 1

Clinical Conditions Associated with Castleman's Disease

Dermatologic
Pemphigus vulgaris (PC)
Cutaneous Kaposi sarcoma (HV) #
Glomeruloid hemangioma (PC) #

Hematologic
Refractory anemia (PC)
Lupus anticoagulant (PC)
Autoimmune cytopenias (PC)
Thrombotic thrombocytopenic purpura (HV)
Myelofibrosis (HV)

Renal
Nephrotic syndrome (PC)
Acute renal failure (PC)
Glomerulonephritis (PC)

Neurological
Peripheral neuropathy (PC)
Pseudotumor cerebri (PC, HV) #
Myasthenia gravis (HV)

Oncologic
Malignant lymphoma (PC, HV)
Osteosclerotic myeloma (PC)
Extramedullary plasmacytoma (PC)
Nodal Kaposi sarcoma (PC)
Gamma heavy chain disease (HV)

Miscellaneous
Temporal arteritis (HV)
Pericardial effusion (HV)
Bronchiolitis obliterans (HV)
Recurrent pleural effusion (HV)
Amyloidosis (PC)
Growth retardation (PC)
POEMS syndrome (PC)*
Peliosis hepatis (PC)

PC = plasma-cell type; HV = hyaline-vascular variant
* POEMS syndrome = polyneuropathy, organomegaly, endocrinopathy, Monoclonal (M) protein, and skin changes
# Associated with multicentric Castleman's disease.
(Refs. 2, 4, 7, 8, 27, 40, 49, 55–71).

TABLE 2

Comparison between Clinical Features of the Localized Variant and Multicentric Variant of Castleman's Disease.

Factor	Localized	Multicentric
Age range (yr)	12 – 72	19 – 85
Median age (yr)	23.5	56
Manifestation	Incidental, "mass effect"	Fever, weight loss, pruritus
Histologic features	HV, PC, HV-PC	PC, HV, HV-PC
Lymph node distribution	Central	Peripheral
Organomegaly	Absent	Present
Premalignant potential	Occasionally	Frequently
Clinical course	Benign	Aggressive
Treatment	Surgical excision	Chemotherapy
Prognosis	100% 5-yr survival	Guarded, 26-mo median
Differential diagnosis	Follicular lymphomas, other causes of adenopathy, AIDS, KS.	Follicular lymphoma, AIL, POEMS, Osteosclerotic myeloma, AIDS, KS.

AIDS = acquired immunodeficiency syndrome; AIL = angioimmunoblastic lymphadenopathy; HV = hyaline-vascular variant; PC = plasma-cell variant; HV-PC = mixed-cell variant; POEMS = polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes;
KS = Kaposi sarcoma.

References (1, 2, 4, 7 – 10, 13, 14, 26, 27, 45, 49, 51 – 53).

Laboratory studies commonly reveal anemia, an increased erythrocyte sedimentation rate, polyclonal hypergammaglobulinemia, granulocytosis, and bone marrow plasmacytosis (42). The multicentric variant of CD is clinically more aggressive than the localized variant and follows one of four courses: relapse and remission, stable and persistent, rapidly fatal, or transformation into malignant lymphoma (40).

Historical, clinical and laboratory findings are not useful in predicting the outcome or clinical course of individual patients. One study suggests that the presence of peripheral neuropathy is associated with resistance to therapy and a poor prognosis (45). Most patients with multicentric Castleman's disease have the plasma-cell form (3, 40, 46).

Disseminated thoracic Castleman's disease appears on chest radiographs as bilateral mediastinal widening (35, 43, 47). Focal mediastinal masses are rare. The anterior mediastinum is commonly effected. CT scanning reveals diffuse adenopathy involving multiple mediastinal compartments. The nodes typically are 1 – 6 cm in diameter and of homogeneous attenuation on unenhanced images (33). Associated findings such as splenomegaly or ascites are common (47). Multicentric plasma-cell Castleman's disease rarely presents with reticulonodular opacities on chest radiographs (48). Unlike the localized plasma-cell type of Castleman's disease, which is amenable to surgical excision and has a favorable prognosis (4), the multicentric variant necessitates systemic therapy and is associated with a poor outcome (40, 45, 49). The overall mortality rate is about 50%, with a median survival of 26 months (40). The most common cause of death is sepsis or lymphoma. Patients with multicentric Castleman's disease of either histological type have a poor prognosis (40, 46, 49, 50) in spite of treatment with a combination of radiation therapy, corticosteroids, and chemotherapy. Several immunosuppressive agents (cyclophosphamide, azathioprine) have been used in the treatment of multicentric disease, with anecdotal reports of efficacy (40, 51 – 53).

No regimen is consistently effective in achieving durable remission (40). Radiotherapy alone has been used in isolated cases (53). In view of the poor prognosis of multicentric Castleman's disease, an aggressive management approach with intensive chemotherapy is recommended (52).

After extensive review of the literature, this appears to be the first report in English of a patient with both Castleman's syndrome and superior vena cava thrombosis. Aiba et al. reported, in Japanese, a case of Castleman's disease and superior vena cava syndrome (54). Their patient received chemotherapy and irradiation. The exact cause of the association between the two conditions is not clear. We speculate that the large right hilar mass compressed the superior vena cava, which induced the intravascular thrombosis. Further progression of the thrombotic process in the adjacent veins did not occur when the hilar mass was removed. Repeat CT scan 6 months later showed no evidence of disease and the patient is clinically well.

The various hematological and coagulation disturbances described in relation to Castleman's disease are: autoimmune cytopenias (55), refractory anemia (56), thrombocytopenic purpura (57), lupus anticoagulant (58), and myelofibrosis (59). These manifestations are usually associated with the plasma-cell variant of Castleman's disease. In our case, no coagulation abnormality was detected.

Conclusion

Castleman's disease is an uncommon cause of lymphadenopathy, and must be considered after all other causes have been eliminated. Several neoplastic, autoimmune, infectious diseases can mimic Castleman's disease. Follow-up and periodic evaluation is necessary to detect the malignant lesions. Close communication between the clinician and the pathologist is essential to arrive at the correct diagnosis. The malignant potential of the disease and its possible multicentricity must be kept in mind in order to plan appropriate treatment. The optimal therapeutic regimen for Castleman's disease is unknown. Local disease can be cured with local resection, with an excellent prognosis. For individuals who are poor surgical candidates, radiation therapy can be used. MCD of either histological type has a poor prognosis. Treatment in this situation consists of combination chemotherapy, radiation, and corticosteroids. The finding of thrombi within the superior vena cava and the right brachiocephalic vein is extremely unusual and was thought to be related to compression of these vessels by a large right hilar mass.

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